Exhibit 1

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REVIEW ARTICLE

Pharmaceutical Applications of Solid Dispersion Systems

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Keyphrases ☐ Solid dispersion systems—review ☐ Dispersions, solid systems—review ☐ Absorption kinetics—solid dispersion systems, review ☐ Dosage forms, fast-release—solid dispersion systems, review

CONTENTS

HISTORICAL BACKGROUND

The effect of the particle size of drugs on their dissolution rates and biological availability was reviewed comprehensively by Fincher (1). For drugs whose GI absorption is rate limited by dissolution, reduction of the particle size generally increases the rate of absorption and/or total bioavailability. This commonly occurs for drugs with poor water solubility. For example, the therapeutic dose of griseofulvin was reduced to 50% by micronization (2), and it also produced a more constant and reliable blood level. The commercial dose of spironolactone was also decreased to half by just a slight reduction of particle size (3). Such enhancement of drug absorption could further be increased several fold if a micronized product was used (3, 4).

Particle-size reduction is usually achieved by: (*a*) conventional trituration and grinding; (*b*) ball milling; (*c*) fluid energy micronization; (*d*) controlled precipitation by change of solvents or temperature, application of ultrasonic waves (5–7), and spray drying (8); (*e*)

administration of liquid solutions from which, upon dilution with gastric fluids, the dissolved drug may precipitate in very fine particles (9); and (*f*) administration of water-soluble salts of poorly soluble compounds from which the parent, neutral forms may precipitate in ultrafine form in GI fluids. Although the reduction of particle size can be easily and directly accomplished by the first four methods (*a–d*), the resultant fine particles may not produce the expected faster dissolution and absorption. This primarily results from the possible aggregation and agglomeration of the fine particles due to their increased surface energy and the subsequent stronger van der Waals' attraction between nonpolar molecules. This was demonstrated by Lin *et al.* (10), who showed that the *in vitro* dissolution rates of micronized griseofulvin and glutethimide were slower than those of their coarser particles. However, the opposite finding for griseofulvin was reported by Chiou and Riegelman (11, 12). Another inherent disadvantage of these pure fine powders of poorly soluble drugs is their poor wettability in water. The wetting of powders is the first step for them to dissolve and sometimes disperse in fluids (13). Furthermore, drugs with plastic properties are difficult to subdivide by methods *a–c*. They have more tendency to stick together, even if fine powders can be produced by controlled precipitation.

Theoretically, the solvent method (*c*) seems to be an ideal approach in achieving particle-size reduction. However, it is not frequently employed in the commercial market due to such reasons as selection of a nontoxic solvent, limitation to drugs with a low dose, and high costs of production. The water-soluble salts of many poorly soluble acidic or basic drugs have been widely used clinically as solid dosage forms. Indeed, they have been shown frequently to produce better absorption than their parent forms. It has been shown that the potassium or sodium salts may react with atmospheric carbon dioxide and water to precipitate out poorly soluble parent compounds. This occurs especially on the outer layer of a dosage form and thereby retards rates of dissolution and absorption. This precipitation effect is believed to be responsible for the slower *in vitro* dissolution rates and the lower novobiocin plasma levels in dogs following the oral administration of its soluble sodium salt rather than the less soluble amorphous form of the parent compound (14). The reported failure of the clinical response from three commercial capsule dosage forms containing sodium diphenylhydantoin may be caused by the same reason (15). In addition, the alkalinity of some salts may cause epigastric distress following administration (16).

In 1961, a unique approach of solid dispersion to reduce the particle size and increase rates of dissolution and absorption was first demonstrated by Sekiguchi and Obi (17). They proposed the formation of a eutectic mixture of a poorly soluble drug such as sulfathiazole with a physiologically inert, easily soluble carrier such as urea. The eutectic mixture was prepared by melting the physical mixture of the drug and the carrier, followed by a rapid solidification process. Upon exposure to aqueous fluids, the active drug was expected to be released into the fluids as fine, dispersed particles because of the fine dispersion of the drug in the solid eutectic mixture and the rapid dissolution of the soluble matrix. Levy (9) and Kanig (18) subsequently noted the possibility of using a solid solution approach in which a drug is dispersed molecularly in a soluble carrier. In a series of reports in 1965–1966, Goldberg *et al.* (19–22) presented a detailed experimental and theoretical discussion of advantages of the solid solution over the eutectic mixture.

In 1965, Tachibana and Nakamura (23) reported a novel method for preparing aqueous colloidal dispersions of β-carotene by using water-soluble polymers such as polyvinylpyrrolidone. They dissolved the drug and the polymer carrier in a common solvent and then evaporated the solvent completely. A colloidal dispersion was obtained when the coprecipitate was exposed to water. In 1966, Mayersohn and Gibaldi (24) demonstrated that the dissolution rate of griseofulvin could be markedly enhanced when dispersed in polyvinylpyrrolidone by the same solvent method. The mechanisms of increased dissolution rates of drugs, solid dispersed in polyvinylpyrrolidone carriers, were thoroughly discussed by Simonelli *et al.* (25, 26). Chiou and Riegelman (11) recently advocated the application of glass solutions to increase dissolution rates. The significance of the solid dispersion technique was strengthened by the demonstration of Chiou and Riegelman (27–29) of the fast and almost complete absorption of the insoluble griseofulvin in man and dogs while the commercial micronized griseofulvin was incompletely absorbed (30–60%). They used polyethylene glycol 6000 as a dispersion carrier. The main advantages of using water-soluble polymers as carriers are their nontoxicity and general applicability to most drugs.

It is believed that this relatively new field of pharmaceutical technique and principles will play an important role in increasing dissolution, absorption, and therapeutic efficacy of drugs in future dosage forms. Therefore, a thorough understanding of its fast-release principles, methods of preparation, selection of suitable carriers, determination of physical properties, limitations, and disadvantages will be essential in the practical and effective application of this approach. The main purpose of this article is to review critically the hitherto limited pharmaceutical literature pertinent to this area. Since a great amount of excellent work on solid dispersion systems has been accumulated in the sciences of metallurgy, geology, and chemistry, a brief summary of some of these findings would be extremely helpful in the future study and understanding of pharmaceutical applications of solid dispersion systems. One major objective of this review article is to introduce and correlate these works to possible pharmaceutical applications.

In addition to absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications which remain to be further explored. It is possible that such a technique can be used to obtain a homogeneous distribution of a small amount of drugs at solid state, to stabilize unstable drugs, to dispense liquid or gaseous compounds, to formulate a fast-release priming dose in a sustained-release dosage form, and to formulate sustained-

release or prolonged-release regimens of soluble drugs by using poorly soluble or insoluble carriers. It is hoped that this review paper will stimulate interest and research in these unexplored areas.

DEFINITION AND METHODS OF PREPARATION OF SOLID DISPERSIONS

Definition—It seems suitable here to define the term "solid dispersions" as used in this paper. The term refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting–solvent method. The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. The solid dispersions may also be called solid-state dispersions, as first used by Mayersohn and Gibaldi (24). The term "coprecipitates" has also been frequently used to refer to those preparations obtained by the solvent methods such as coprecipitates of sulfathiazole–polyvinylpyrrolidone (25) and reserpine–polyvinylpyrrolidone (30). Since the dissolution rate of a component from a surface is affected by the second component in a multiple-component mixture (31), the selection of the carrier has an ultimate influence on the dissolution characteristics of the dispersed drug. Therefore, a water-soluble carrier results in a fast release of the drug from the matrix, and a poorly soluble or insoluble carrier leads to a slower release of the drug from the matrix. This review paper primarily deals with fast-release solid dispersions, although some principles discussed later may also be applied to slow-release solid dispersion systems. To achieve a faster release of a drug from the matrix, it is generally necessary that the active drug be a minor component in the dispersion system in terms of the percent weight (not on molar basis).

Methods of Preparation—*Melting Method*—The melting or fusion method was first proposed by Sekiguchi and Obi (17) to prepare fast-release solid dispersion dosage forms. The physical mixture of a drug and a water-soluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved. Such a technique was subsequently employed with some modification by Goldberg *et al.* (20–22) and Chiou and Riegelman (11). To facilitate faster solidification, the homogeneous melt was poured in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. The solidified masses of drug–polyethylene glycol polymer systems were often found to require storage of 1 or more days in a desiccator at ambient temperatures for hardening and ease of powdering (11). Some systems, such as griseofulvin and citric acid, were found to harden more rapidly if kept at 37° or higher temperatures (11, 32).

The main advantages of this direct melting method are its simplicity and economy. In addition, a supersaturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature (34). Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. Similarly, a much finer dispersion of crystallites was obtained for systems of simple eutectic mixtures if such quenching techniques were used (34, 35). The disadvantage is that many substances, either drugs or carriers, may decompose or evaporate during the fusion process at high temperatures. For example, succinic acid, used as a carrier for griseofulvin (21), is quite volatile and may also partially decompose by dehydration near its melting point (36). However, this evaporation problem can be avoided if the physical mixture is heated in a sealed container. Melting under vacuum or a blanket of an inert gas such as nitrogen may be employed to prevent oxidation of the drug or carrier (37).

The melting point of a binary system is dependent upon its composition, *i.e.*, the selection of the carrier and the weight fraction of the drug in the system (33). By proper control, the melting point (the temperature at which the mixture completely melts) of a binary system may be much lower than the melting points of its two components. Under such a condition, this simple melting method can still be used to prepare solid dispersions, even if the pure drug may undergo decomposition at or near its melting point. This principle was used to prepare solid dispersions of steroids and a cardiac glycoside in polyethylene glycol 6000 (38) and that of griseofulvin in pentaerythritol (11).

Solvent Method—This method has been used for a long time in the preparation of solid solutions or mixed crystals of organic or inorganic compounds (33). They are prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent. This method was used to prepare solid dispersions of β-carotene–polyvinylpyrrolidone (23), griseofulvin–polyvinylpyrrolidone (24), sulfathiazole–polyvinylpyrrolidone (25), steroid–polyvinylpyrrolidone (26), reserpine–polyvinylpyrrolidone (30), and reserpine–deoxycholic acid (39).

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents. However, some disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing liquid solvent, the possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the drug, the selection of a common volatile solvent, and the difficulty of reproducing crystal forms. In addition, a supersaturation of the solute in the solid system cannot be attained except in a system showing highly viscous properties, as is discussed later. It must be emphasized that the suitability of the solvent method to prepare simple eutectics or partial solid solutions remains to be studied further because their final physical properties may be quite different from those obtained by the melting method.

Melting–Solvent Method—It was shown recently that 5–10% (w/w) of liquid compounds could be incorporated into polyethylene glycol 6000 without significant loss of its solid property (40). Hence, it is

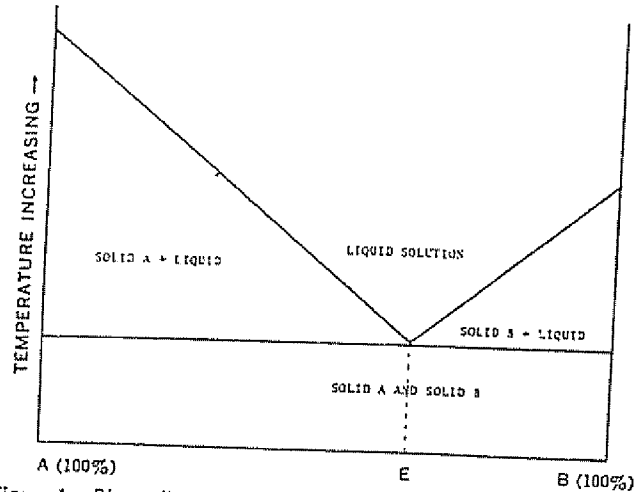


Figure 1—*Phase diagram of a simple eutectic mixture with negligible solid solubility.*

possible to prepare solid dispersions by first dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, obtainable below 70°, without removing the liquid solvent. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol. The polymorphic form of the drug precipitated in the solid dispersion may be affected by the liquid solvent used. Such a unique method possesses the advantages of both the melting and solvent methods. Unfortunately, from a practical standpoint, it is only limited to drugs with a low therapeutic dose, *e.g.*, below 50 mg. The feasibility of this method was demonstrated on spironolactone–polyethylene glycol 6000 and griseofulvin–polyethylene glycol 6000 systems (41). Its application to other drugs and carriers, however, remains to be explored.

CLASSIFICATION AND FAST-RELEASE MECHANISMS

Although solid dispersion systems may include more than two components, for the sake of simplicity and practicality, this article is primarily limited to binary systems. As a measure of the interaction between the two components, 30 different phase diagrams were proposed for binary alloy systems (42). Vasil'ev (43) further classified phase diagrams according to: (*a*) the relative strength of interaction between similar and different atoms, and (*b*) the limiting permissible degree of deformation of the energy field of the liquid solvent or its crystal lattice in the solid state. While it is believed that these classifications can also be applied to most organic drugs, in this article it is felt more appropriate to classify various systems of solid dispersions on the basis of their major fast-release mechanisms. Accordingly, they are discussed in the following six groups: Group 1, simple eutectic mixtures; Group 2, solid solutions; Group 3, glass solutions and glass suspensions; Group 4, amorphous precipitations of a drug in a crystalline carrier; Group 5, compound or complex formations between the drug and the carrier; and Group 6, any combinations among Groups 1–5. The methods used to identify these systems are reviewed in the next section.

Simple Eutectic Mixtures—The simple eutectic mixture is usually prepared from the rapid solidification of the fused liquid of two components which show complete liquid miscibility and negligible solid–solid solubility (33). These properties can be illustrated in a phase diagram (Fig. 1). Thermodynamically, such a system is regarded as an intimately blended physical mixture of its two crystalline components (19, 33, 34).

When a eutectic (Composition E in Fig. 1) composed of a poorly soluble drug is exposed to water or GI fluids, the carrier may be released into aqueous medium in fine crystalline form (17). This is based on the assumption that both components may simultaneously crystallize out in very small particulate sizes (33). The increase of the specific area due to this reduction of particle size generally increases rates of dissolution and oral absorption of poorly soluble drugs. Ultrafine or colloidal crystallites of eutectics can be found in such examples as tin–lead (34) and naphthalene–phenanthrene (44) systems. In addition to the reduction of the crystallite size, the following factors may contribute to the faster dissolution rate of a drug dispersed in the eutectic:

1. An increase in drug solubility may occur if the majority of its solid crystallites are extremely small (45).

2. A possible solubilization effect by the carrier may operate in the microenvironment (diffusion layer) immediately surrounding the drug particle in the early stage of dissolution since the carrier completely dissolves in a short time. This was demonstrated by the faster dissolution rate of acetaminophen from its physical mixture with urea than that of the pure compound with comparable particle size (22). This hypothesis was further supported by a marked increase of acetaminophen solubility in the presence of urea in water (22). A similar rationale was also given to the enhancement of dissolution rates of reserpine from a physical mixture of reserpine and polyvinylpyrrolidone (30).

3. The absence of aggregation and agglomeration between fine crystallites of the pure hydrophobic drug may play a far more important role in increasing rates of dissolution and absorption than is presently recognized by research workers in this field. An aggregate is defined as a particle or an assembly of particles held together by strong inter- or intramolecular or atomic cohesive forces (46). Usually the aggregate is stable to high-speed mixing or ultrasonic forces. An agglomerate is defined as a gathering of two or more particles and/or aggregates held together by relatively weak cohesive forces. In many cases, these forces are due to an electrostatic surface charge generated during handling or processing operations (46). It is also likely that these electrostatic forces may be involved only in bringing particles together, but they are not responsible for holding them together. Such agglomeration is more severe for very finely divided particles (about 0.1 μ) due to the greater specific surface charge. Although the agglomerates may be broken, their dispersion in the mildly stirred GI fluids may not be very efficient. As mentioned previously, these problems of aggregation and agglomeration are most

detrimental to the application and efficacy of pure fine particles because their effective specific surface area is markedly reduced[1]. Serious drawbacks of aggregation and agglomeration and lumping in the dissolution medium between pure drug particles are, however, rarely present in most solid dispersion systems because the individually dispersed particles are surrounded in the matrix by carrier particles. It must be emphasized that the aggregation and agglomeration of the solid dispersion powders may not significantly affect the dissolution of the drug, which can still disintegrate quickly due to the more rapid dissolution of the soluble carrier. Such a unique advantage of solid dispersion systems was demonstrated in the *in vivo* absorption (28, 29) of griseofulvin when dispersed in polyethylene glycol 6000 (10% w/w) and compressed into a hard tablet. As discussed later, the 10% griseofulvin dispersion in polyethylene glycol 6000 contains at least half of the griseofulvin in the finely dispersed crystalline form. The dissolution rates of the pure and dispersed griseofulvin are shown in Fig. 2.

4. Excellent wettability and dispersibility of a drug from a eutectic or other solid dispersion system prepared with a water-soluble matrix result in an increased dissolution rate of the drug in aqueous media. This is due to the fact that each single crystallite of the drug is very intimately encircled by the soluble carrier which can readily dissolve and cause the water to contact and wet the drug particle. As a consequence, a fine homogeneous suspension of a drug can be easily obtained with minimum stirring (17). These striking advantages were observed by the authors with various drug–polyethylene glycol solid dispersions. In contrast, the aggregates and agglomerates of poorly soluble pure powders are surrounded by the nonpolar air, which is hard to penetrate or displace by water.

5. An increased rate of dissolution and absorption may also occur if a drug crystallizes in a metastable form after solidification from the fused solution. A metastable, crystalline form has a higher solubility which, in turn, leads to a faster dissolution rate according to the well-known Noyes–Whitney equation. Interested readers should consult an excellent review paper by Haleblian and McCrone (47) on the pharmaceutical applications of polymorphism. The high possibility of the polymorphic crystallization during the preparation of solid dispersions can be seen from the facts that many compounds can exhibit polymorphism. For example, 67% of steroids, 43% of sulfonamides, and 63% of barbiturates were shown to exhibit polymorphism in an extensive survey by Kuhnert-Brandstätter (48). It must be noted that the existence of a different polymorphic form or forms results in a phase diagram differing from that shown in Fig. 1 (47).

[1] Peculiar examples were encountered by the authors when 125 mg. of the pure micronized griseofulvin and 100–200-mesh griseofulvin, loosely packed in a No. 3 gelatin capsule, were studied for dissolution rates in 18 l. of water at 37° under a fairly vigorous stirring condition (*Reference 11*; the capsule kept in a cylindrical container, 5 × 3 cm., made of No. 8 mesh stainless steel screen and moved by a standard USP disintegration apparatus). The griseofulvin lumped together as a single mass even after 4–6 hr. of study, and dissolution only took place at the surface of the mass. This phenomenon was also noted in a commercial capsule product of griseofulvin.

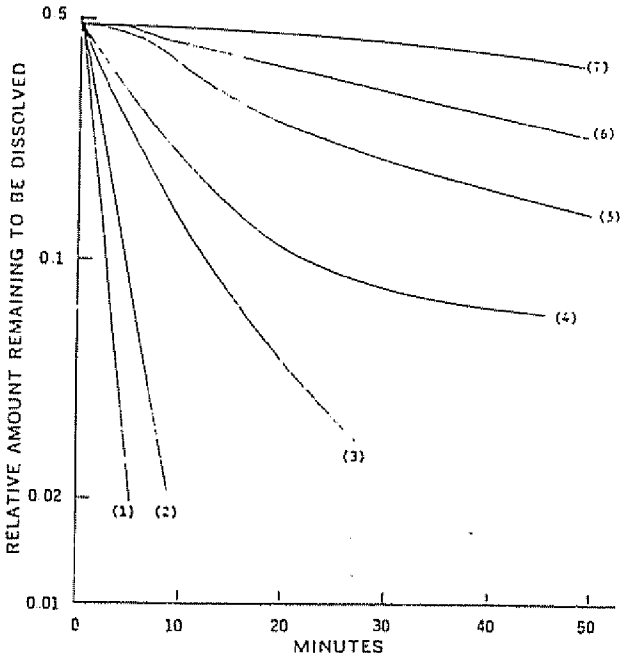


Figure 2—*Griseofulvin dissolution-rate data (amount remaining to be dissolved) from 125 mg. in 18 l. of water at 36.7°. Key: (1), 10% griseofulvin–polyethylene glycol 6000 powder; (2), 20% griseofulvin–polyethylene glycol 6000 powder; (3), 40% griseofulvin–polyethylene glycol 6000 powder; (4), wetted, micronized griseofulvin powder; (5), nonwetted, micronized griseofulvin powder; (6), micronized griseofulvin in capsule; and (7), 100–200-mesh griseofulvin powder in capsule.*

In addition to the possible aforementioned differences between the eutectics and the physical or mechanical mixtures, the rapidly crystallized (quenched) eutectics are characterized by increased hardness (49). This was explained on the basis of a high degree of strain resulting from the action of mechanical forces. The effect of such increased hardness on the dissolution rate, however, remains to be explored. Savchenko (49) advocated that a eutectic is formed by some sort of loose molecular or atomic interaction which does not involve the formation of a chemical bond. This is thought to relate to some of the changes in physical properties of eutectic alloys such as a reduction in electrical conductivity, vapor pressure, and thermal effects. It must be emphasized that a slow process of cooling and solidification from the melt may not result in fine dispersion of the phases (49), which is primarily responsible for the higher dissolution rate of the drug.

The composition of a eutectic may have a significant effect on the particle size of the crystallite. If it is made up of a high weight fraction of drug, an ultrafine crystallization of the drug may not be obtained. This is logical if one expects that the higher the dilution, the finer the crystalline size of its precipitate. This probably accounts for the failure to find an increased dissolution rate of acetaminophen from the eutectic with urea which contains 52% of the acetaminophen (20). It is believed that the hardening effect of the eutectic may also play a role in retarding its dissolution.

Recently, Chiou (50) contended that the system of chloramphenicol–urea should be described as a simple eutectic mixture with negligible solid–solid solubility

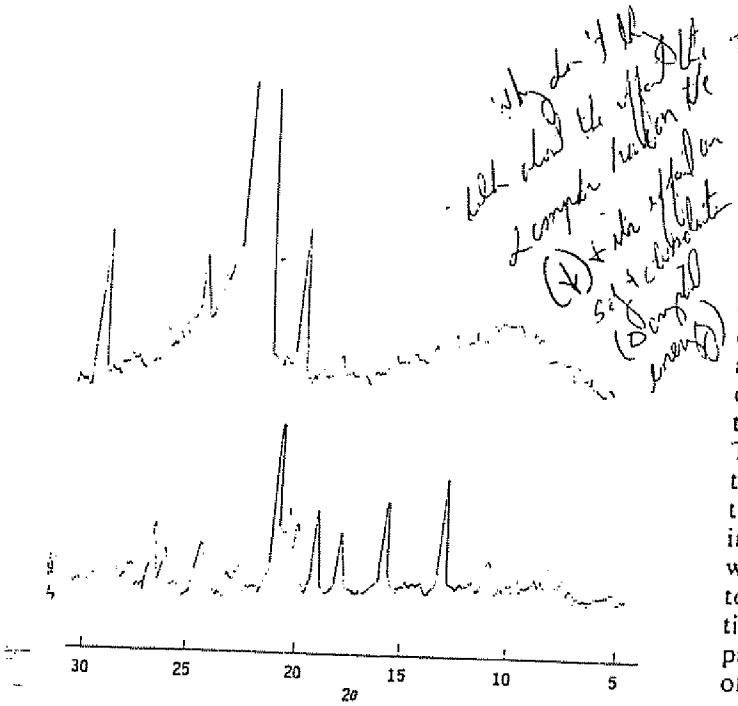


Figure 3—*X-ray diffraction spectra of pure chloramphenicol (bottom) and pure urea (top).*

rather than an extensive, partial solid solution as previously proposed by Sekiguchi *et al.* (51) and Goldberg *et al.* (22). This appears to be supported by differential thermal analysis (DTA) and X-ray diffraction data. The endothermic peaks of 2.5 and 97% chloramphenicol resolidified samples at the eutectic temperature (51) indicate that the samples started to thaw at that temperature. If their compositions did not belong to a simple eutectic system, then the thaw points should begin at a higher temperature (52).

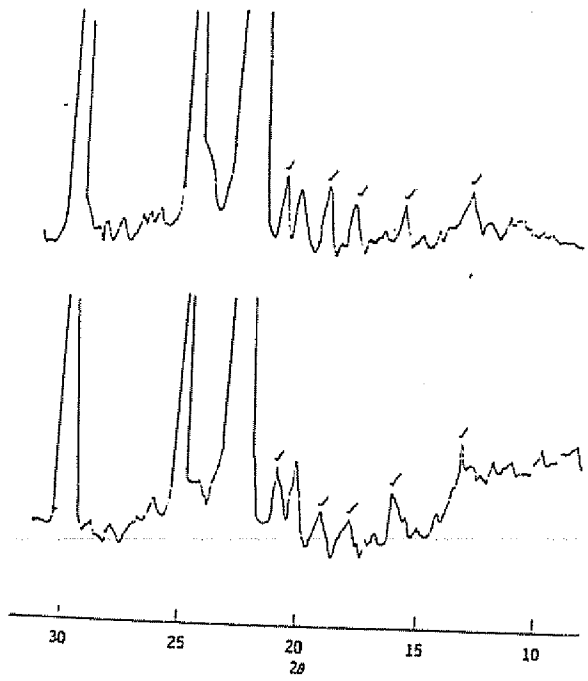


Figure 4—*X-ray diffraction spectra of a physical mixture of 10% chloramphenicol–90% urea (bottom) and resolidified fused mixture of 10% chloramphenicol–90% urea (top). Arrows indicate diffraction peaks due to the presence of chloramphenicol crystallites.*

In the previously proposed phase diagram, chloramphenicol was shown to dissolve in the solid urea at a concentration of 25% (w/w). To investigate this system further, diffraction spectra were obtained from a Norelco X-ray diffractometer using CuKα radiation. The spectra of pure chloramphenicol, pure urea, and the physical mixture and resolidified mixture of 10% chloramphenicol are shown in Figs. 3 and 4. The presence of the typical X-ray diffraction peaks of chloramphenicol in the freshly prepared, quenched sample of 10% chloramphenicol unmistakably indicates that the sample is not a solid solution but a eutectic mixture. The height of these peaks, which are comparable with those obtained from the physical mixture, also indicates the negligibility of solid solubility. The slight increase in dissolution rate of the eutectic (75% chloramphenicol w/w) over the pure chloramphenicol (22) may be due to a coarser particle size of chloramphenicol crystallization and the hardening effect of the eutectic. The small particle size of the precipitate at the lower concentration of the chloramphenicol, however, may be primarily contributory to the reported attainment of supersaturation and marked enhancement of dissolution rate from 25% solid dispersion (22, 51). It is further expected that a much faster dissolution rate may be obtained from the lower concentrations of the chloramphenicol in such a eutectic mixture.

From their microthermal microscope studies, Goldberg *et al.* (21) reported that griseofulvin, a water-insoluble antibiotic, forms a solid solution with succinic acid at a concentration of 25% w/w. The dissolution rate from such dispersions was found to be several times higher than that of the micronized griseofulvin. Furthermore, a supersaturation of about 250% of the solubility was also observed. Chiou and Niazi (53) recently concluded from their DTA and X-ray diffraction studies that such a binary system is a simple eutectic mixture with negligible solid solubility. The dissolution rates of griseofulvin were found to increase as the concentration of griseofulvin in the solid dispersion decreased.

Solid Solutions—A solid solution, compared to a liquid solution, is made up of a solid solute dissolved in a solid solvent. It is often called a mixed crystal because the two components crystallize together in a homogeneous one-phase system (33). In their theoretical paper, Goldberg *et al.* (19) suggested that a solid solution of a poorly soluble drug in a rapidly soluble carrier achieves a faster dissolution rate than a eutectic mixture because the particle size of the drug in the solid solution is reduced to a minimum state, *i.e.*, its molecular size. In other words, the dissolution of the drug takes place in the solid state prior to its exposure to the liquid medium. In addition to such maximum size reduction, other factors such as Factors 1–4 discussed under *Simple Eutectic Mixtures* may contribute to increased rates of dissolution and absorption of drugs dispersed in solid solutions. It must be emphasized that the advantage of a solid solution may not be so significant if the solid solution is exposed to a medium with a volume much less capable to dissolve all the drug. Under these conditions, a drug may precipitate. However, due to the maximum particle-size reduction

in the solid solution and to the possible solubilization effect of the carrier in the microenvironmental diffusion layer of bulk fluids, the drug may temporarily result in a high supersaturation of the bulk fluid. Obviously, this is temporary and would lead to precipitation if the drug is not being absorbed or removed by other processes.

Solid solutions can generally be classified according to the extent of miscibility between the two components or the crystalline structure of the solid solution (33, 34, 54). Based on the former criterion, they can be divided into two groups: continuous (or isomorphous, unlimited, complete) solid solutions and discontinuous (or limited, restricted, partial, incomplete) solid solutions. According to the latter criterion, they can also be classified into two groups: substitutional solid solutions and interstitial solid solutions. The important physical properties of each group are reviewed briefly.

Continuous Solid Solution—In this system, the two components are miscible or soluble at solid state in all proportions (Fig. 5). No established solid solution of this kind has been shown to exhibit fast-release dissolution properties, although it is theoretically possible. It is obvious that a faster dissolution rate would be obtained if the drug is present as a minor component. However, the presence of a small amount of the soluble carrier in the crystalline lattice of the poorly soluble drug may also produce a dissolution rate faster than the pure compound with similar particle size. This may be due to a small number of the neighboring drug molecules holding the dissolving drug molecule after the rapid dissolution of the neighboring water-soluble carrier. The total lattice energy of the continuous solid solution at various compositions theoretically should be greater than that of either pure component, because the strength of bond between the two different components at the solid state, U_{AB}, should be greater than that between the same species of molecules, U_{AA} and U_{BB}, in order to form a continuous solid solution (33). The solid solution above the temperature of the miscibility gap, as shown in Fig. 5, is also thermodynamically stable, with a free energy lower than that anticipated from the mixture law (54, 55). The miscibility gap noted in Fig. 5 may occur as a result of limited solid-state solubility at lower temperatures. The implication of this phenomenon is discussed later in this article.

Discontinuous Solid Solution—In contrast to the continuous solid solution, there is only a limited solubility of a solute in a solid solvent in this group of solid solutions. This can be best depicted in a standard phase diagram (Fig. 6). The regions of solid solutions in this diagram are shown as the α and β regions. Each component shown is capable of dissolving the other component to a certain degree above the eutectic temperature. However, as the temperature is lowered, the solid solution regions become narrower. The implication of the decreasing solubility with declining temperature is discussed later. The free energy of a stable, limited solid solution is also lower than that of the pure solvent (55).

In reality, some solid-state solubility can be expected for all two-component systems (19, 34). However, the degree of solubility is usually small enough to be considered negligible. Goldberg *et al.* (19) suggested that, for practical purposes, solubility of greater than 5% of one component in the other could be considered to be a solid solution. It is felt that such a criterion is not adequate. Sensitive instruments now allow the detection of solid solution formation below a 5% level. Furthermore, many drugs with low therapeutic doses (*e.g.*, below 25 mg.) can be practically incorporated into solid solutions at concentrations of less than 5%.

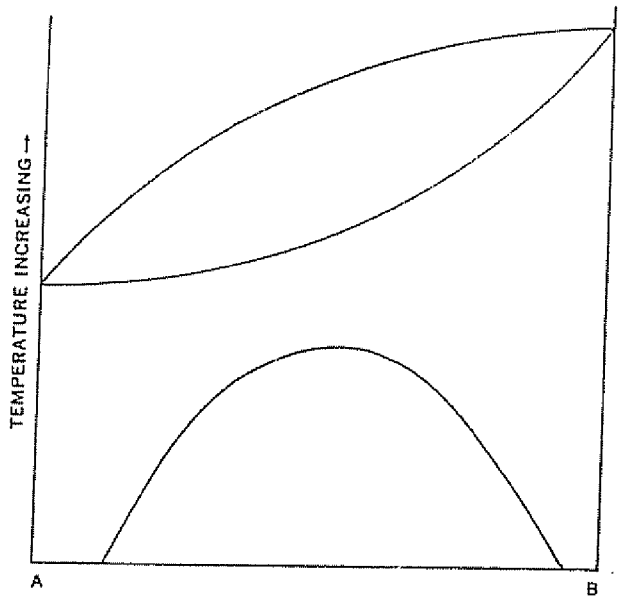


Figure 5—*A typical phase diagram of continuous solid solution of a binary system, A and B. The lowest curve indicates a solubility gap at lower temperatures.*

The phase diagram of a sulfathiazole–urea binary system was studied by thermal analysis (17). It was interpreted as a system of limited solid solution, in which the maximum solubility of sulfathiazole is about 10% w/w and that of urea is about 8% w/w (19). The eutectic composition is located at 52% of sulfathiazole. Therefore, the eutectic of this system is

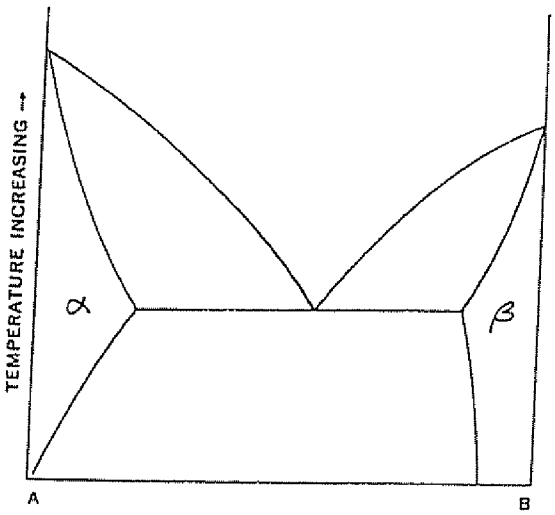


Figure 6—*A typical phase diagram of a discontinuous solid solution of a binary system, A and B. α and β are regions of solid solution formation*

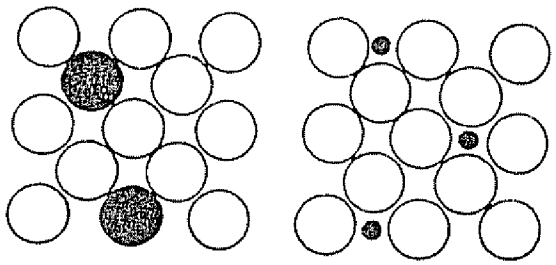


Figure 7—*Right diagram shows the formation of an interstitial solid solution, and left diagram shows the formation of a substitutional solid solution. Dark circles indicate solute atoms or molecules, while open circles indicate solvent atoms or molecules (from* Reference 54, *reprinted with permission).*

theoretically a physical mixture of two solid solutions, α and β. The faster absorption rates found in man with this eutectic mixture were claimed to be primarily due to these solid solutions. However, it was also recently noted by Chiou and Niazi (56), from their X-ray diffraction studies, that sulfathiazole is mainly present as an amorphous form (more correctly a glass solution) in the freshly prepared eutectic. No significant amount of sulfathiazole was found to crystallize when kept at 27° for 2 weeks. It was proposed that such an amorphous form, with a solubility much greater than the crystalline form (25), was an important contributing factor to the increased rate of dissolution and absorption.

Substitutional Solid Solution—In this type of solid solution, the solute molecule substitutes for the solvent molecule in the crystal lattice of the solid solvent. A schematic diagram is shown in Fig. 7. It can form a continuous or discontinuous solid solution. The size and steric factors of the solute molecule were shown to play a decisive role in the formation of solid solutions (33, 34, 43, 54). The size of the solute and the solvent molecule should be as close as possible. According to the Hume-Ruthery rule (54, 57), an extensive solid solution can be formed only when the effective diameter of the solute differs less than 15% from that of the solvent. This has been experimentally proven in a variety of solid solutions of metals and inorganic compounds.

Timmermans (60) proposed a term called the degree of molecular isomorphism to express the degree of similarity of the shape of the two components. He superimposed the two molecules and calculated the overlapping volume, r, and the nonoverlapping volume, Δ. The degree of molecular isomorphism, e, is then equal to $1 - \Delta/r$. From his extensive studies of phase diagrams of organic compounds, he found that wide or complete solubility required the value of e to be around 0.9. Examples of continuous solid solutions of systems include mixtures of *p*-dibromobenzene–*p*-chlorobromobenzene (61) and anthracene–acenaphthene (62).

The distortion of the crystal lattice of the solvent by the steric effect or chemical interaction (63) is also important. The solubility of the solute increases until the distortion of the lattice field of the solvent by the solute molecule can no longer be tolerated. For example, naphthalene (59) can form solid solutions with its β-derivatives substituted with halogens, hydroxyl, or amino groups but it only forms eutectic mixtures with its α-substituted derivatives. However, e values are the same for the pairs of α- and β-derivatives with naphthalene.

Frequently, water-insoluble drugs contain halogens, hydroxyl, methyl, methoxy, or other small functional groups. It might be possible to synthesize relatively inert soluble congeners by substituting a specific functional group which will change the physical properties with minimal changes in the degree of molecular isomorphism. It is expected that the insoluble drugs and the congeners can possibly form wide ranges of solid solutions due to their similarity in size and shape. Under such conditions, the relatively inactive soluble derivatives can serve as carriers for the active drugs. Such a combination may result in more rapid dissolution and absorption.

It is well known that globular or plastic compounds form a wide range of solid solutions above their plastic points. For example, pairs of cyclopentane–2,2-dimethylbutane (64) and chemically unrelated methane and argon (65) form continuous solid solutions at appropriate temperatures. Typical properties of globular or plastic compounds are (64): (*a*) low entropy of fusion, usually less than 5 e.u.; (*b*) high triple-point temperature and pressure; (*c*) crystals, usually of cubic or hexagonal symmetry, which are clear (almost glasslike), tacky, and easily deformed; and (*d*) one or more energetic transitions in the solid state. The reasons for their mutual solubility are the similarity in their symmetry and almost free rotation (hence, low lattice energy) above their plastic points. Since plastic compounds have the lowest lattice energy and strain, it is reasonable to expect that they will more easily accommodate all kinds of molecules in their crystal lattice.

Pentaerythritol, a typical plastic compound (64) with an entropy of fusion of 3.2 e.u., was selected as a carrier to disperse griseofulvin (11). The 10% griseofulvin dispersion was found to dissolve much faster than micronized griseofulvin. In addition, a supersaturation was rapidly obtained when an excess amount was studied. Its potential usage as a carrier for other drugs, however, remains to be further explored. A similar carrier, pentaerythritol tetraacetate, was also shown to enhance the dissolution rate of griseofulvin (11). The phase diagrams of both systems have not been established. A comprehensive listing of globular molecules and some skeleton structures with low entropies of fusion was compiled by Ubbelohde (66). Interested readers should consult it for their possible applications.

Interstitial Solid Solution—In this type of solid solution, the solute (guest) molecule occupies the interstitial space of the solvent (host) lattice. A schematic diagram is shown in Fig. 7. It usually forms only a discontinuous (limited) solid solution. The size of the solute is critical in order to fit into the interstices (34, 54). It was found that the apparent diameter of the solute atom should be less than 0.59 that of the solvent (54) in order to obtain an extensive interstitial solid solution of metals. From this, one may calculate that the volume of the solute should be less than 20% of

the solvent. It is likely that the principle can also be applied to organic compounds. Water-soluble crystalline polymers of high molecular weight appear to be logical choices for this type of solid solution of insoluble drugs, since the molecular weight of most organic drugs is usually less than 1000. Low toxicity and lack of absorption from the GI tract are the advantages of polymer carriers.

Polyethylene glycols of 4000, 6000, and 20,000 molecular weights are crystalline, water-soluble polymers with two parallel helixes in a unit cell (67). It is predicted that significant amounts of drug can be trapped in the helical interstitial space when polyethylene glycol–drug melts are solidified. Such systems were prepared using griseofulvin, digitoxin, methyltestosterone, prednisolone acetate, and hydrocortisone acetate in the matrix of polyethylene glycol 6000. They all possess a fast rate of dissolution (11, 38). The results of these dissolution studies, except for griseofulvin, are summarized in Table I. The griseofulvin dispersed in polyethylene glycol 4000 and 20,000 was also shown to have a marked increase in dissolution rate (11). Indomethacin dispersed in polyethylene glycol 6000 was also shown to produce a faster dissolution rate (68).

In addition to the large molecular size of the polymers favoring the formation of thermodynamically stable interstitial solid solutions, other factors such as high viscosity, supercooling, and physical–chemical interaction between the drugs and the polymers may contribute to the formation of metastable solid solutions if the drug–polyethylene glycol melt is solidified rapidly. The melt of polyethylene glycol polymers is highly viscous, even at a temperature of 200° (67). Furthermore, the viscosity increases rapidly with the decrease in temperature. Therefore, as drug–polyethylene glycol melt is allowed to solidify quickly, the crystallization of the drug is retarded due to reduced solute migration and the difficulty in nucleation of the drug in the viscous medium (11, 64, 69).

Although the melting points of some polyethylene glycol polymers are higher than 50°, they can often be supercooled to below 40° (11). Such supercooling phenomena were also observed with the drug–polyethylene glycol mixture. For example, it was found feasible to supercool 10, 20, and even 40% of griseofulvin in polyethylene glycol 4000 or 6000 to about 40° before solidification started, although their upper melting points (when mixtures completely melt) ranged from about 150 to 200°. The possible physical or chemical interaction between drugs and polyethylene glycol polymers has been well documented, as demonstrated by their solubilization effect in the aqueous medium (45, 72). It is believed that such interaction may also exist in the drug–polyethylene glycol melt and may contribute to the retardation of crystallization of the pure drugs. In the case of griseofulvin, its solubility was found to increase onefold in the 7% (w/w) polyethylene glycol 6000 aqueous solution (41).

The possibility of the existence of a metastable solid solution of a drug in polyethylene glycol was investigated in quenched 5% griseofulvin–95% polyethylene glycol 4000 and 5% griseofulvin–95% polyethylene glycol 6000 (41). The freshly quenched samples of both systems showed no noticeable X-ray diffraction peaks of the crystalline griseofulvin, while their powdered samples exhibited such peaks. It was suggested that the powdering process might cause some of the supersaturated griseofulvin in the metastable solid solution to precipitate out. Therefore, the solid solubility of griseofulvin in polyethylene glycol 4000 or 6000 is much less than 5%. The X-ray diffraction spectra of the griseofulvin–polyethylene glycol 6000 system are shown in Figs. 8 and 9. Similar findings were also reported for the 10% indomethacin–90% polyethylene glycol 6000 solid dispersion (68). In 10 and 20% griseofulvin dispersed in polyethylene glycol 6000, both the pulverized and nonpulverized quenched samples showed the diffraction spectra of crystalline griseofulvin. This is because the concentrations of griseofulvin now exceeded its maximum solid solubility in the polyethylene glycol.

In addition to working as a universal solvent for the formation of stable or metastable limited solid solutions of most drugs, the polyethylene glycol can also be expected to produce an ultrafine or colloidal crystallization of the pure drug if its concentration is much greater than its solid solubility and the drug–polyethylene glycol melt is solidified rapidly (11). This is mainly due to the difficulty of growth of the crystallite in a highly viscous medium and the short time interval for the completion of solidification. This is often referred to by some surface chemists as the transition from primary to secondary nucleation. The phenomenon is well known and is taken advantage of in the preparation of single crystals in microelectronics. It is also the method by which doped crystals are prepared to render specific physical properties in a system in which a material is crystallized in a retarded manner due to solute depletion in the immediate environment affecting crystal growth. The highly possible physical–chemical interaction between the drug and polyethylene glycol may also play a role in preventing the crystalline growth. Such a contention is indirectly supported by a recent study of the ability of polyvinylpyrrolidone to inhibit the crystalline growth of sulfathiazole and methylprednisolone in

Table I—Twenty, Fifty, and Seventy Percent Dissolution Times for Selected Drugs in Various Physical Forms in Half-Saturation Dissolution Test

Preparations	T_{20}, min.	T_{50}, min.	T_{70}, min.
Pure prednisolone acetate[a]	8.0	45.0	—
Fused mixture of prednisolone[a] acetate–polyethylene glycol 6000 (5:95 w/w)	≪1.0	≪1.0	~0.6
Pure 17-methyltestosterone	2.0	12.0	28.0
Fused mixtures of 17-methyltestosterone–polyethylene glycol 6000 (5:95 w/w)	≪1.0	≪1.0	~0.6
Pure hydrocortisone acetate	20.0	—	—
Fused mixture of hydrocortisone acetate–polyethylene glycol 6000 (5:95 w/w)	≪1.0	≪1.0	1.5
Pure microcrystalline digitoxin	15.0	80.0	—
Fused mixture of digitoxin–polyethylene glycol 6000 (2:98 w/w)	≪1.0	≪1.0	0.3–0.5

[a] This test system utilized only 30% saturation.

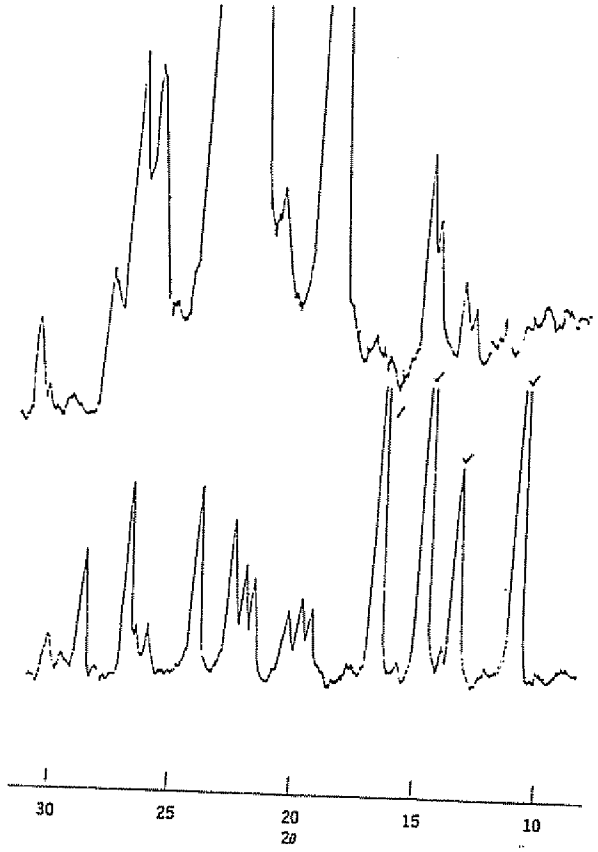


Figure 8—*X-ray diffraction spectra of pure griseofulvin (bottom) and pure polyethylene glycol 6000 powders (top).*

water, even at a very low concentration (73). The adsorption of the polyvinylpyrrolidone on the crystalline surface was used to explain such a phenomenon. It seems logical to assume that the polyethylene glycol polymer may also act as a protective colloid in retarding the coagulation, aggregation, or coarsening of the fine crystallites before solidification. The possibility of an ultrafine or colloidal dispersion of drugs in polyethylene glycol polymers is demonstrated by the fact that even the solid dispersion of 40% griseofulvin–60% polyethylene glycol 6000 showed a faster dissolution rate than the wetted micronized griseofulvin (11). It is believed that this rationale for employing polyethylene glycol polymers as ideal solid-dispersing carriers may also be applied to other soluble polymers. As mentioned, the short interval of solidification is critical in the formation of metastable solid solutions from the viscous melt of drug–polyethylene glycol systems. Therefore, in the solvent method of preparation, the control of temperature and time of evaporation are very important to the final physical properties of the solid dispersions (11). It was found that big crystals of griseofulvin were formed if the griseofulvin–polyethylene glycol 6000–ethanol mixture was kept at high temperatures (*e.g.*, 120°) for a relatively long period (0.5–2 hr.).

A patent was obtained for the use of water-soluble polymers such as polyethylene glycol, polyoxyethylene esters or ethers, polyoxyethylene sorbitan esters, or their mixtures that form solid solutions of insoluble estrogens for preparation of pessary dosage forms (74). The estrogen was claimed to be precipitated in an extremely fine state of subdivision when the preparation was placed in water. The concentration of the drug preferred was below 20%. This patent may not be known to many research workers in this area, and no experimental data in the pharmaceutical literature could be found to support the claim. One interesting suggestion in the patent is that the inclusion of effervescent materials, such as combinations of sodium bicarbonate and citric or tartaric acid, would increase the distribution (or dispersion) of the drug upon exposure to an aqueous medium. No oral application of such dosage forms was advocated.

Glass Solutions and Glass Suspensions—The concept of formation of a glass solution (75) was first introduced by Chiou and Riegelman (11) as another potential modification of dosage forms in increasing drug dissolution and absorption. Since physical–chemical properties of glass solutions have not been adequately discussed in the pharmaceutical literature, they are briefly reviewed in this article. A glass solution is a homogeneous, glassy system in which a solute dissolves in a glassy solvent. The familiar term "glass," however, can be used to describe either a pure chemical or a mixture of chemicals (window glass is a mixture of inorganic oxides) in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt (76, 77). It is characterized by transparency and brittleness below the glass-transforming temperature, T_g. On heating, it softens progressively and continuously without a sharp melting point. This is primarily due to the facts that the chemical bonds in the glass differ considerably in length and, therefore, in strength and that there is no one temperature at which all the bonds become loosened simultaneously (34). The glassy form of pure compounds can often be transformed to a crystalline state upon heating. It is likely that such transformation may also

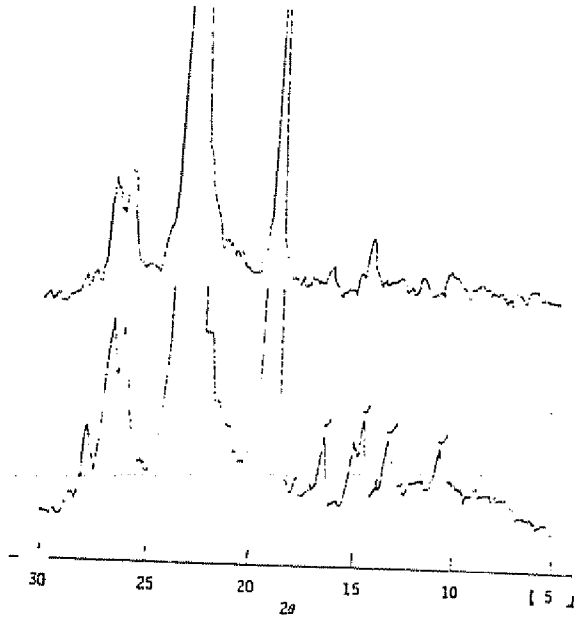


Figure 9—*X-ray diffraction spectra of solid dispersion of 5% griseofulvin–95% polyethylene glycol 6000. The top spectrum was obtained from a nonpowdered sample, and the bottom spectrum was obtained from a powdered sample.*

occur in some glassy solutions. Usually the thermodynamic properties of a glass, such as specific volume, specific heat, viscosity, refractive index, compressibility, and thermal conductivity, all show critical change around the temperature T_g.

The relation of the volume between the glassy, liquid, and solid states is shown in Fig. 10 (76). As the liquid is cooled through the freezing point, T_f, it may either freeze into a crystalline solid, with a discontinuous change in volume, or it may continue as a supercooled liquid below this temperature. Many substances may behave in either way, according to circumstances. For example, supercooling is increasingly likely to occur if the presence of any nuclei is carefully avoided. The viscosity of a supercooled liquid may be so great that the behavior of the material starts to appear indistinguishable from that of an ordinary solid. If the liquid is further cooled rapidly, a change in slope of the volume–temperature curve occurs and the new slope is often nearly the same as that of the corresponding curve for the crystal. The temperature at which the curve changes slope is called the glass-transforming temperature, T_g. Below T_g, the curve is no longer an equilibrium curve. Therefore, a glass or glass solution is metastable. It is also interesting to note that any liquid or supercooled liquid whose viscosity is greater than 10^{13} poises is generally called a glass (75).

A crystalline solid possesses both long-range and short-range orders of structure, whereas a glass or liquid has a structure only with a short-range order (76, 78). This can be differentiated easily by X-ray diffraction methods. A glass or liquid can only produce weak and diffuse diffraction effects, while crystallites can give strong and sharp diffraction effects (76, 79). In this sense, a glass is also amorphous to X-ray diffraction.

Many compounds have been shown to be able to form glasses readily upon cooling from the liquid state. These compounds include sucrose, glucose, ethanol, and 3-methylhexane (66). Glass formation is common in many polyhydroxyl molecules such as sugars, presumably due to their strong hydrogen bonding which may prevent their crystallization (64). Polymers possessing linear, flexible chains can freeze into a glassy state of transparency and brittleness (66). Glass formation can occur for the pure substance itself or when in the presence of other components. If a water-insoluble drug forms a glass solution with a water-soluble, glass-forming carrier, then the *in situ* dissolved drug is released into the aqueous medium rapidly because the carrier quickly dissolves upon exposure to the aqueous medium (11).

There is usually a relatively strong chemical binding between the solute and the solvent in the solid solution (4), while the lattice energy in the glass solution is expected to be much less because of its similarity with the liquid solution. Similarly, the dissolution rate from a crystal is usually faster than from an amorphous or glassy solid of the same chemical identity. Therefore, if everything is equal, the dissolution rate of drugs in the glass solution should be theoretically faster than that in the solid solution. There is another important advantage of glass solutions over solid solutions. When

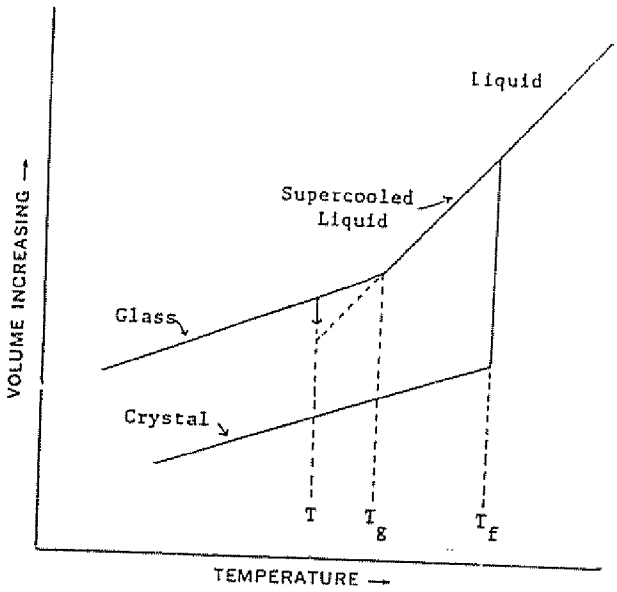


Figure 10—*Relation between the glassy, liquid, and solid states (from* Reference 76, *reprinted with permission).*

the content of the solute exceeds the solubility in both solutions at ambient temperatures, the particle size of crystallization of the solute is much smaller in the glass solution due to the difficult growth of the crystal in its viscous medium. A higher supersaturation of the drug in the glass solution is also more likely to take place if the extremely viscous melt is cooled rapidly.

Citric acid, a normal constituent of animals, was found capable of glass formation (11). The melt is highly viscous and can be drawn into a thread or sheet[2]. After standing at 37° for a few days, a hard, brittle, and transparent glass can be obtained. However, this glassy state was transformed into a crystalline state after months of standing at room temperature. Glassy solutions were obtained after the cooling of melts of 5 and 20% griseofulvin (11), 10% phenobarbital, and 10% hexobarbital (12). A marked increase in the dissolution rate of griseofulvin in the citric acid glass solution was reported (11). The potential usage of citric acid and the previously mentioned glass-forming polyhydroxyl compounds as water-soluble carriers remains to be investigated.

The properties of a glass may be related to the method of solidification or cooling (79). The particle-size distribution in the crystallization of benzophenone in hydrocarbon glass was shown to be a function of the cooling rate, ranging from being invisible to opaque in appearance as the rate of cooling was prolonged (80). A term of "glass suspension" is proposed here to refer to a mixture in which precipitated particles are suspended in a glassy solvent.

Pure polyvinylpyrrolidone and some other polymers dissolved in the organic solvents may become glassy after the evaporation of the solvents. It is possible that the precipitation of drugs introduced into the system is inhibited due to the increase in viscosity as the solvents evaporate. Such inhibition may also be

[2] It is entirely possible that the formation of the citric acid glass is partially due to decomposition of some molecules by dehydration into aconitic acid.

Table II—Dissolution Studies of Griseofulvin[a]

Sample	Relative Dissolution Rate 1 min.	4 min.
Micronized griseofulvin	1.0	1.0
Griseofulvin–chloroform solvate	0.5	0.4
Griseofulvin–polyvinylpyrrolidone (1:5)	6.1	5.1
Griseofulvin–polyvinylpyrrolidone (1:10)	7.2	6.1
Griseofulvin–polyvinylpyrrolidone (1:20)	11.0	7.3

[a] Obtained from *Reference 24*.

facilitated by the possible complexation between the drug and the polymer. Thereby, a transparent, brittle, glassy solution is formed. This principle of glass formation probably best explains the rationale behind the polymer approach suggested by Tachibana and Nakamura (23) and Mayersohn and Gibaldi (24). The amorphous and glassy property of polyvinylpyrrolidone is also evidenced by its diffuse, broadening, X-ray diffraction spectra (25, 41). Evidence for molecular dispersion of drugs in polyvinylpyrrolidone (*i.e.*, glass solution) is provided by use of the UV method for β-carotene (23), high-resolution electron microscope method for iopanoic acid (41), and X-ray diffraction method for sulfathiazole (25) and iopanoic acid (41). By the same reasoning as was discussed for the polyethylene glycol carrier, the crystallite size of the drug may also be very fine if the drug concentration greatly exceeds its solubility in polyvinylpyrrolidone. The crystallization was found to occur at the higher concentration of sulfathiazole by the X-ray diffraction method (25). Amorphous precipitation of iopanoic acid was also found in the 50% iopanoic acid–50% polyvinylpyrrolidone 10,000 coprecipitate by the electron microscope technique (41). These systems also appear to be metastable since crystallization has been initiated in fissures or cracks in the glass on standing.

Due to the chemical stability of polyvinylpyrrolidone to heat (81) and its high melting point (probably decomposing before melting at a temperature beyond 250°), the drug–polyvinylpyrrolidone solid dispersions can only be prepared by the solvent method. Polyvinylpyrrolidone is also soluble in a variety of organic solvents (81), an advantage in accommodating various drugs which possess limited solubility properties. The marked enhancement of griseofulvin dissolution from the coprecipitate is shown in Table II (24). Almost 100% supersaturation was also obtained in 1 min. Such a striking effect is also reported for reserpine (30). For a 1:6 reserpine–polyvinylpyrrolidone coprecipitate, a 200-fold increase in dissolution was found in comparison with the equal particle size of the pure drug. The dissolution rates of the drugs decreased as the concentrations of the drugs in the coprecipitates increased in both systems. Probably this is mainly due to the increase of particle size of the drugs in the higher concentration compositions (30).

Table III—Experimental Relative Release Rates of Sulfathiazole as a Function of Polyvinylpyrrolidone Weight Fraction[a]

Polyvinylpyrrolidone Weight Fraction	Absolute Sulfathiazole Release Rate—Initial	Limiting	Relative[b] Sulfathiazole Release Rate—Initial	Limiting
0.25 (3:1)	0.135	—	—	—
0.40 (1.5:1)	0.510	0.140	3.78	1.02
0.50 (1:1)	0.520	0.140	3.85	1.04
0.60 (1:1.5)	0.520	—	3.85	—
0.67 (1:2)	0.680	—	5.04	—
0.75 (1:3)	1.155	—	8.90	—
0.83 (1:5)	1.100	—	8.15	—
0.91 (1:10)	0.934	—	6.91	—
0.95 (1:20)	0.450	—	3.33	—

[a] Obtained from *Reference 25*. [b] Relative to a pure sulfathiazole crystalline Form I tablet

Simonelli *et al.* (25) presented thorough experimental studies to elucidate the dissolution mechanisms from a constant surface for compressed tablets of polyvinylpyrrolidone–sulfathiazole coprecipitates. The enhancement of dissolution rate was found to be a function of the molecular weight of polyvinylpyrrolidone, the concentration of sulfathiazole in the coprecipitates, and, in some instances, the dissolution medium and time. A model was presented to describe dissolution mechanisms of the coprecipitates and physical mixtures over a wide range of composition. For the coprecipitates, it was concluded that the sulfathiazole was the controlling external layer at lower polyvinylpyrrolidone weight fractions and the polyvinylpyrrolidone at higher weight fractions. For details, interested readers are urged to consult this detailed original paper. The relative release rates of sulfathiazole as a function of the polyvinylpyrrolidone weight fraction are shown in Table III. In 40 and 50% polyvinylpyrrolidone samples, the release rates were not linear but changed with time.

Several points arising from the Simonelli *et al.* (25) paper seem to warrant further discussion. The possible effect of molecular dispersion (in this case, glass solution) and colloidal dispersion of sulfathiazole in the polyvinylpyrrolidone on the dissolution rate of sulfathiazole was ignored by the authors. The necessity of taking the molecular dispersion into account for the enhancement of dissolution rate from tablet forms with a constant surface was clearly demonstrated by an approximately 10-fold increase in dissolution rate from a solid solution of 10% indomethacin–90% polyethylene glycol 6000 and also a threefold increase from a solid solution of 5% sulfathiazole–95% urea over the physical mixtures with the same chemical composition (68). A tablet made of 10% griseofulvin–90% succinic acid eutectic mixture was also found to dissolve about threefold faster than the mechanical mixture of 10% micronized griseofulvin–90% succinic acid (53). Such effects are more likely to take place at the higher weight fractions of a carrier.

In their dissolution model, Simonelli *et al.* (25) proposed polyvinylpyrrolidone as the controlling external layer at higher polyvinylpyrrolidone fractions. The identity of the controlling layer can easily be determined by comparing the relative movement of the solid–liquid boundary of each component (25, 31). On the basis of the dissolution data shown in the original article, in the first 20 min, the ratios of the movement of polyvinylpyrrolidone over sulfathiazole at compositions of 1:20, 1:10, and 1:5 (sulfathiazole–polyvinylpyrrolidone) were found to be all close to 1. These ratios indicate that both components were released

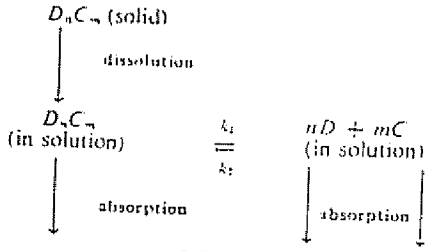
almost simultaneously from the tablets. This finding is contradictory to the dissolution model proposed by Higuchi (31), which defines a congruent dissolution from a binary mixture tablet only taking place at a single, fixed composition. This is valid only when the solubilities of the two components remain constant. It is well known that the magnitude of solubility increases as the particle size reduces to submicron or colloidal range (45). In the solid solution or glass solution of a drug in the soluble carrier, the maximum concentration of a drug at the dissolution interface is undoubtedly much higher than the regular solubility. Furthermore, colloidal or molecular particulates probably cannot aggregate or agglomerate into bigger particles in the short time that they exist at the dissolution surface. If this is true, it is difficult to define the solubility value at different weight fractions of solid dispersions.

The theoretical dissolution rates of sulfathiazole in the higher polyvinylpyrrolidone fractions, calculated according to the model proposed by Simonelli *et al.* (25), imply that similar dissolution rates also can be obtained from the physical mixtures. Although this has not been proved experimentally, it is regarded as unlikely in light of the striking increase of dissolution rates of the drugs dispersed in polyvinylpyrrolidone in powdered forms (24, 30).

Amorphous Precipitations in a Crystalline Carrier—Instead of forming a simple eutectic mixture in which both the drug and the carrier crystallize simultaneously from a melting or a solvent method of preparation, the drug may also precipitate out in an amorphous form in the crystalline carrier. Since the amorphous form is the highest energy form of a pure drug, it should, under almost all conditions[3], produce faster dissolution and absorption rates than the crystalline form whether the crystals are or are not dispersed in a carrier. Amorphous novobiocin has 10-fold higher solubility than its crystalline form (82). A much faster dissolution rate and higher blood levels were also found for the amorphous form of novobiocin (82). As discussed previously, the amorphous sulfathiazole dispersed in the crystalline urea was believed to be a primary contributing factor in increasing its oral absorption in man (17). It is postulated that a drug with a high supercooling property has more tendency to solidify as an amorphous form in the presence of a carrier.

Compound or Complex Formations—In a strict sense, the modification of a dosage form by a compound or complex formation (D_nC_m) between a drug (D) and an inert soluble carrier (C) should not be classified under the applications of solid dispersion systems. Nevertheless, due to their frequent occurrence during preparation of solid dispersions by the standard methods, it seems worthwhile to review them here briefly.

The dissolution and absorption of a drug into the body from a complex or a compound are schematically shown in Scheme I. It is clear from Scheme I that the availability of a drug depends on the solubility, the dissociation constant, and the intrinsic absorption rate



Scheme I

of the complex. Although the water-soluble polymers have been considered as ideal carriers for the solid dispersion of poorly soluble drugs, the implication of the possible complexation should not be overlooked. Polyvinylpyrrolidone was shown to retard the pharmacological action of numerous compounds such as penicillin, novocaine, prostigmine, hexobarbital, quinine (83), and hexylresorcinol (84). The formation of an insoluble complex between phenobarbital and polyethylene glycol 4000 or 6000 was shown to reduce rates of dissolution and permeation of phenobarbital through everted guts of rats (85). The complexation between griseofulvin and polyethylene glycol 6000 may be thought to occur on the basis of the traditional solubility study. (The solubility is increased onefold by the presence of 7% polyethylene glycol 6000 in water.) Such a water-soluble weak complex apparently did not retard the oral absorption of griseofulvin in man and dogs (27–29). It is believed that in comparison with pure, insoluble, solid drugs, the rates of dissolution and GI absorption can be increased by the formation of a soluble complex with a low association constant.

The compound formation among simple organic chemicals seems more common than expected. Among 12 phase diagrams, Sekiguchi *et al.* (51) found 11 cases of compound formations. Guillory *et al.* (86) reported four compound formations out of nine phase diagrams studied. However, the occurrence of these compound formations, which previously took place at melt state, does not necessarily mean that they will also take place in a liquid medium. On the other hand, the existence of compound or complex formation in a liquid medium does not predicate its occurrence in the solid state. This is shown in the griseofulvin–succinic acid system. Although the solubility of griseofulvin was increased markedly by the succinic acid in water (approximately onefold per 1.5% succinic acid), their interaction could not be detected by the phase diagram study (53).

Combinations and Miscellaneous Mechanisms—Quite often a solid dispersion does not entirely belong to any of the four groups discussed but is made up of combinations of different groups. Therefore, the observed increase in dissolution and absorption rates may be the contribution of different mechanisms. The griseofulvin dispersed at high concentrations in polyethylene glycol may exist as individual molecules and as microcrystalline particles. The sulfathiazole dispersed at high concentrations in polyvinylpyrrolidone may be present as individual sulfathiazole and sulfathiazole–polyvinylpyrrolidone complex molecules, amorphous and polymorphic sulfathiazole, and possibly an amorphous sulfathiazole–polyvinylpyrrolidone complex.

[3] A large amorphous mass with entrapped air probably will not dissolve faster than microcrystals dispersed in a water-soluble carrier.

The coprecipitates of reserpine with bile steroids such as deoxycholic acid (39), cholic acid, lithocholic acid, and 3,12,24-trihydroxycholane (87) were shown to increase blepharoptotic activity of reserpine in mice. The exact physical properties of such systems have not been elucidated. A decrease in the particle size of reserpine in the coprecipitates was proposed from the *in vitro* dissolution studies (88, 89). The ability of these carriers to reduce the surface tension of aqueous fluids led Stoll *et al.* (89) to propose that the carriers may also facilitate the wetting and, hence, the dissolution rate of reserpine. Since these bile steroids can form clathrate compounds (inclusion compounds) with a variety of organic molecules (90), it is possible that this may also occur with reserpine and thus cause molecular or ultrafine dispersion of reserpine in the hollow channels of the clathrates.

METHODS OF DETERMINATION OF TYPES OF SOLID DISPERSION SYSTEMS

Many methods are available that can contribute information regarding the physical nature of a solid dispersion system. In many instances, a combination of two or more methods is required to study its complete picture. The advantages and disadvantages of each method are briefly expounded here.

Thermal Analysis—This is the most common approach used to study the physicochemical interactions of two or more component systems. Several modified techniques utilizing the principle of change of thermal energy as a function of temperature are discussed separately.

Cooling-Curve Method—In this method, the physical mixtures of various compositions are heated until a homogeneous melt is obtained. The temperature of the mixture is then recorded as a function of time. From a series of temperature–time curves, the phase diagram can be established (33, 34). The method suffers from many inherent disadvantages. It is time consuming, it requires a relatively large amount of sample, and changes in slopes can be missed, especially if cooling takes place rapidly (86). In addition, the method cannot be applied to samples that decompose after melting. It is also difficult to detect samples with small solid–solid solubility. This method was recently used to determine phase diagrams of deoxycholic acid–menadione and caffeine–phenobarbital (86).

Thaw-Melt Method—In this method, a sample of a solidified mixture in a capillary melting-point tube is heated gradually. The thaw point is referred to a temperature on crossing a solidus line (33). This simple method was used extensively by Rheinboldt (91), Rheinboldt and Kircheisen (92, 93), and Guillory *et al.* (86). A stirring device in the capillary tube was employed for more accurate results by Sekiguchi *et al.* (94). The stirring facilitates the attainment of a homogeneous system; however, such stirring only affects the melting point and not the thaw point. In differentiating between a simple eutectic system and a limited solid solution, the diagnostic point lies at the thaw point. Therefore, the usage of this more complicated device is not necessary for such a purpose. The principal drawback of this thaw-melt method is that it depends on a subjective observation and, thereby, is not highly reproducible (86). This is especially serious for the determination of thaw points. A range of six degrees of variation was reported in the study of thaw points of a chloramphenicol–urea system (51). Furthermore, a suitable, upper range of melting points is only limited to about 300° due to the problem associated with capability of visualization (86, 94). The sample used for study may also be prepared from merely the physical mixture or the evaporated mixture obtained after removing the liquid solvent from the solution (94). Thaw points are often found at lower temperatures from the samples of physical mixtures, while the melting points are not affected (94). A special quenching method is proposed for samples exhibiting supercooling properties (33). A mixture that has not completely solidified results in lower thaw and melting points upon reheating. This was observed in the eutectic composition of a sulfathiazole–urea system (56).

Thermomicroscopic Method—Goldberg *et al.* (20) used polarized microscopy with a hot stage to study phase diagrams of binary systems. The physical mixture is placed on a slide covered with a cover slip and sealed with silicone grease to prevent sublimation. The mixture is heated until it completely liquifies. After cooling, the mixture is heated at the rate of 4°/min. The thaw and melting points are then determined by visual observation. The advantages of this method are that it is simple and it requires only a small amount of sample. However, it suffers some disadvantages by often being subjective, limited to thermally stable compounds, and potentially inhomogeneous in distribution after resolidification. Furthermore, the melting of isotropic crystals often cannot be detected accurately under a polarizing microscope (95). The existence of a limited solid solution of griseofulvin in succinic acid determined by this method (21) appears to have been disproved by the DTA and X-ray diffraction method (53). The Köfler contact method, also utilizing polarizing microscopes, was proposed to establish various forms of phase diagrams (95). However, the usage of such a technique seems to require a good knowledge of crystallography.

DTA—DTA is an effective thermal method for studying phase equilibria of either a pure compound or a mixture. Differential effects, associated with physical or chemical changes, are automatically recorded as a function of temperature or time as the substance is heated at a uniform rate (96). In addition to thawing and melting, polymorphic transitions, evaporation, sublimation, desolvation, and other types of decomposition can be detected. Apparatus permitting direct observation of samples during heating were used to facilitate the observation of any physical–chemical changes (97).

The greatest advantage of using this technique is in constructing phase diagrams of high reproducibility; a higher temperature range is permitted, and greater resolution results (52). A sample size of less than 1 mg. can be used for measurement with some commercial instruments. Although the sensitivity and accuracy of the DTA thermograms can be influenced by many

factors such as sample size, heating rate, sample geometry, thermal conductivity of the sample container, and method of measurement of the sample temperature, these variables can be adjusted to optimize the desired characteristics of the DTA apparatus (52).

The DTA method was used extensively to construct phase diagrams of a number of binary systems (51, 52, 86, 98–110). The correlation of DTA data with most frequently encountered phase diagrams is shown in Figs. 11 and 12. This technique is especially valuable in detecting the presence of a small amount of eutectic in the mixture, because its melting at the eutectic temperature can be sensitively detected (98). The observation of such small fractions of melting at eutectic temperature can often be missed when employing thaw-melt or thermomicroscopic methods.

Zone Melting Method—This technique was first introduced in 1952 (111). It has been primarily used for ultrapurification of metals and inorganic and organic compounds. The phase diagram can be constructed for metals and inorganic and organic compounds. A molten zone effected by a heater traverses a cylindrical ingot or solidified melt at a rate of about 0.5–0.001 cm./hr. A mechanical stirring device is also required for the mixing of the liquid in the molten zone. After zone melting is finished, the bar is sectioned and analyzed for its chemical composition. From their chemical compositions and freezing temperatures of the corresponding sections, a phase diagram of a binary or multicomponent system can be constructed. This method is limited to compounds with high thermal stability and low volatility (111, 112). It is especially valuable in determining the exact chemical composition of a eutectic and the minute solid–solid solubility at the eutectic temperature by merely a single pass. The solubility of InSe in InSb was found to be less than 1%; that of InSb in InSe was also found to be less than 1% by this method (113). Many phase diagrams of metal systems have been determined by this method (114–118).

X-Ray Diffraction Method—In this method, the intensity of the X-ray diffraction (or reflection) from a sample is measured as a function of diffraction angles. Counter and film methods detect the diffraction intensity. The advantages and disadvantages of these two methods were well discussed (119, 120). In the former method, a better resolution of diffraction peaks can be obtained, and it is also easier to compare their relative diffraction intensity. However, it requires more sample and has less reliability and more sensitivity to sample preparation and position. The latter method is more sensitive for the detection of weak lines.

The diffraction method is a very important and efficient tool in studying the physical nature of solid dispersions. Recently, it was used to study binary eutectic systems of chloramphenicol–urea (50) and griseofulvin–succinic acid (53). Many phase diagrams of inorganic and metal compounds were also determined by this method (121–125).

In simple eutectic systems, diffraction peaks of each crystalline component can be found in the diffraction spectra. In a substitutional solid solution, the lattice parameter of the solvent crystal is either increased, unchanged, or decreased, depending on the relative

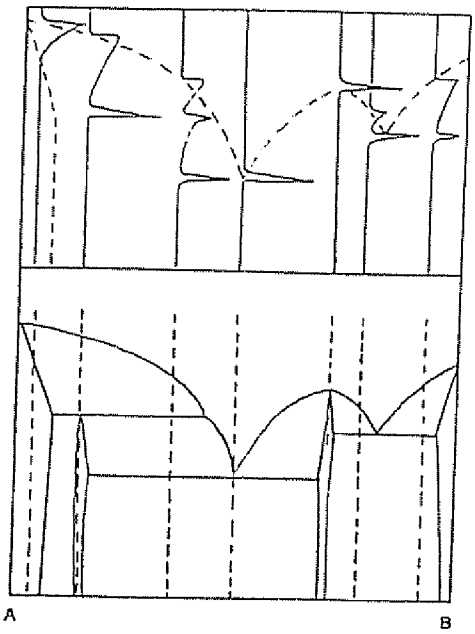


Figure 11—*Typical DTA thermograms corresponding to a hypothetical binary system (from* Reference 52, *reprinted with permission).*

size of the solute atom or molecule (55). However, a gradual shift in the positions of the diffraction lines with changes in composition, which reflects the resulting change in the lattice parameter, is accepted generally as sufficient evidence for the existence of solid solutions. In a system of a continuous solid solution, there will be a shift from the position in one pure component to those in the other (126). The interruption of this smooth change is indicative of immiscibility in the system. The change of lattice parameter, unit cell volume, and density in a continuous solid solution of ammonium chloride–ammonium bromide is shown in Fig. 13. In an interstitial solid solution, the diffraction spectra of the solvent component may or may not

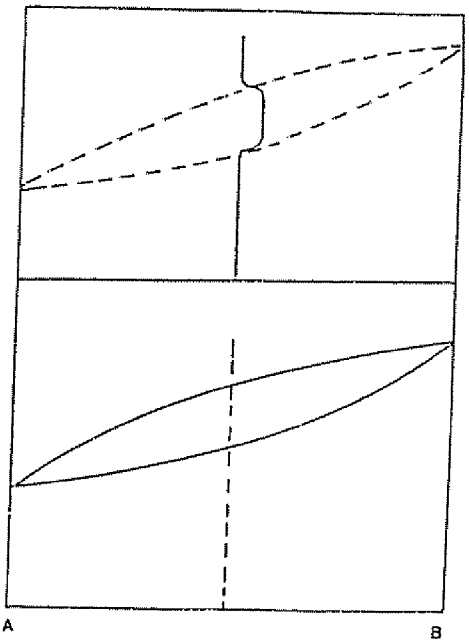


Figure 12—*A DTA thermogram of a continuous solid solution system (from* Reference 52, *reprinted with permission).*

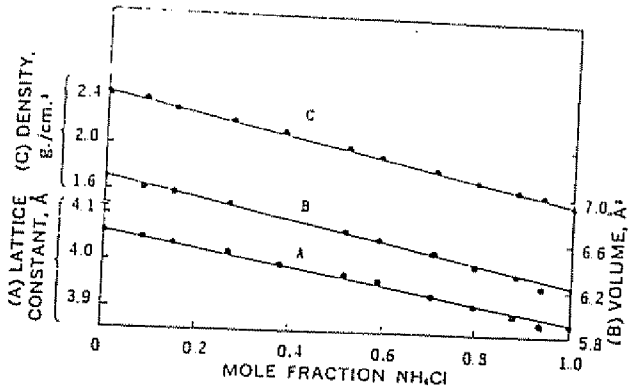


Figure 13—*Variation of composition of continuous solid solution of NH_4Cl–NH_4Br system with (A) lattice constant, Å; (B) unit cell volume, Å³; and (C) density, g./cm.³; low temperature, high-angle data only (from* Reference 125, *Fig. 3, reprinted with permission).*

be changed, while those of the solute component disappear.

The diffraction method is also particularly valuable in detecting compound or complex formation since its spectra or lattice parameters are markedly different from those of pure components. It has been used to disprove the existence of a patented salt formation between penicillin V and tetracycline (126). The biggest drawback of using the diffraction method to study dispersion systems is its frequent inability to differentiate amorphous precipitation from molecular dispersion if the lattice parameter of the solvent component is not changed. This is because of the disappearance of the diffraction peaks or lines of the crystalline solute compound in both systems. This problem is encountered in the lower concentrations of drugs dispersed in polyethylene glycol (41) or polyvinylpyrrolidone (25) polymers. The solidified eutectic of sulfathiazole–urea has a broad (instead of sharp melting point as found for its physical mixture) and lower melting range. This is attributed to the presence of amorphous sulfathiazole. The amorphous form is transformed into a crystalline form after annealing at high temperature, as shown by the appearance of its sharp diffraction peaks (56).

The diffraction method has been used to study quantitatively the concentration of a crystalline component in the mixture (126–128). The ability of this method to quantitate the crystalline component in solid dispersion systems may be limited by its low concentration or weak intrinsic intensity of diffraction. The height of diffraction peaks may be attenuated by a reduction of crystallite size, usually below 0.2 μ. This is also accompanied by a broadening of the peaks (126). An extremely fine crystalline dispersion of sulfathiazole in polyvinylpyrrolidone has also been considered one reason leading to the disappearance of sulfathiazole diffraction peaks (25). Integrated diffraction peak areas were used to study particle-size distribution between 0.002 and 0.2 μ (125).

Microscopic Method—Microscopy has been used quite often to study the polymorphism (47) and morphology of solid dispersions (34, 44, 51, 54, 55, 124, 129). The fine particles of crystallization in the glassy polyvinylpyrrolidone matrix can be readily detected by the polarizing microscope (41). The high resolution of an electron microscope was used to study the dispersed particle size of iopanoic acid in polyvinylpyrrolidone (41). The application of the electron microscope technique is, however, usually limited to chemicals with high atomic numbers (130).

Spectroscopic Method—Visible absorption spectroscopy was used to study the low concentration dispersion of β-carotene in polyvinylpyrrolidone (23). The spectrum of the dispersed β-carotene resembles that of β-carotene dissolved in organic solvents but not that of β-carotene particles. These results indicated that β-carotene is dispersed molecularly in the polymer. The undetected shift of IR bands of the dispersed β-carotene was thought to indicate the absence of the marked interaction between β-carotene and polyvinylpyrrolidone. IR spectroscopy was also used to study the solid solutions of nitrite ion in many inorganic halides such as KBr, NaCl, and KI (131, 132).

Dissolution-Rate Method—The dissolution-rate method was recently proposed by Allen and Kwan (68) to study the degree of crystallinity in solid–solid equilibria, especially in temperature regions below solid–liquid equilibria. The method involves comparing the *in vitro* dissolution rates of the solute component from a constant-surface tablet made from molecular dispersion (*i.e.*, solid or glass solution) with a physical mixture of the same chemical composition. The technique is simple to perform, except that in some binary systems the tablet surface may not remain constant due to the leaching of particles into the dissolution medium. Such difficulty was encountered in the mechanical mixture of the high sulfathiazole to polyvinylpyrrolidone ratio tablets (25), solid dispersion of barbital–polyethylene glycol 6000 system (41), and physical mixture of 10% griseofulvin–90% polyethylene glycol 6000 (41). Tablets made up of 10% sulfathiazole–90% urea physical mixture under various pressures were also found to disintegrate almost immediately in the aqueous medium (56). This was primarily due to the almost instantaneous dissolution of urea into water because the solubility of this small molecule compound in water is very high, approximately 1 g. in 1 ml. The dissolution of 10% sulfathiazole–90% urea solid solution from 10–20-mesh granules was also found to be complete almost immediately upon their exposure to water (56). The almost instantaneous dissolution from such dispersion systems will make them difficult to compare quantitatively with the dissolution from physical mixtures.

The application of this method also requires: (*a*) the observed dissolution rate to be proportional to the surface area, (*b*) a reasonably large difference between the dissolution rate of the physical mixture and the corresponding solid solution, and (*c*) the use of the same polymorphic form of a drug in the tablet of the physical mixture as that precipitated out from the solid dispersion (68). Most commercially available sulfathiazole, which was often used to prepare solid dispersions, is polymorphic Form I, while the precipitated sulfathiazole in the sulfathiazole–urea system is polymorphic Form II (56). The dissolution rate of Form II was found to be 1.6 times higher than that of Form I (56).

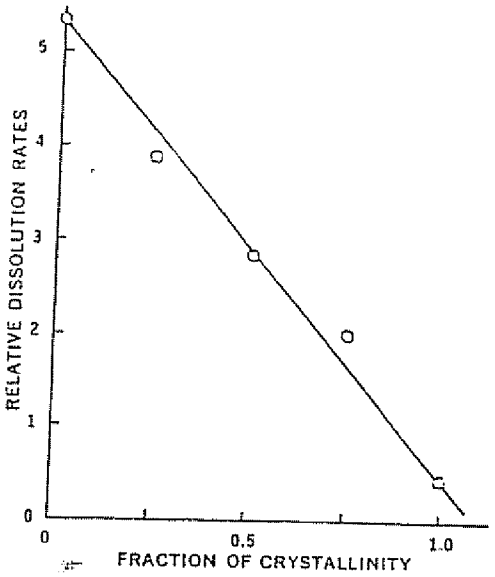


Figure 14—*Dissolution rate* versus *degree of crystallinity of indomethacin in indomethacin–polyethylene glycol 6000 system (from* Reference 68, *reprinted with permission).*

Furthermore, one must assume in this dissolution method that the distribution of particle size (maybe as small as in the subcolloidal range) precipitated from the solid solution or glass solution does not affect the dissolution rate. Such assumption needs to be proved experimentally.

The dissolution-rate method has been shown to be applicable to simulated systems of indomethacin–polyethylene glycol 6000 and sulfathiazole–urea. The data on 10% indomethacin–90% polyethylene glycol 6000 are shown in Fig. 14. The validity of this principle, however, needs further confirmation by other methods.

Thermodynamic Method—The phase diagrams of eutectic and solid solution systems can be constructed on the basis of some thermodynamic parameters (34, 54, 62, 121, 133, 134). A knowledge of heats of fusion, entropies, and partial pressures at various compositions enables one to determine the solubility gap below the solid–liquid equilibrium temperature (133). A solubility gap in the continuous solid solution of the AgBr–NaBr system was also found from thermodynamic data obtained from an electromotive force study by galvanic cells (121). The detailed mathematical discussion of such an approach is beyond the scope of this article.

AGING OF SOLID DISPERSIONS

The solid dispersion appears to be a potential dosage form modification for increasing dissolution and absorption rates of poorly soluble drugs. However, the result of aging or storage under various conditions and the effects on the fast-release characteristics and chemical stabilities have not been reported extensively. Undoubtedly, this will be an interesting and important research subject for pharmaceutical scientists before the wide and long-range practical applications of this unique approach are feasible. The effects of aging in many nonpharmaceutical systems such as alloys and inorganic compounds have been well studied. The purpose of this section is to review these studies with a hope that similar principles and methodologies can be utilized to apply to our systems.

Aging Effects of Eutectic Mixture—It is well known that the dispersed-phase particles tend to coarsen on aging because the interfacial energy of the system is reduced by the concomitant reduction in interface area (129). The phenomenon of particle coarsening was extensively studied both theoretically (135, 136) and experimentally (137–140). This phenomenon occurs in eutectic systems with or without solid solution formation. The extent of coarsening increases with time and aging temperature. The morphology and transparency of a freshly prepared eutectic mixture of naphthalene–phenanthrene were found to change after standing primarily due to recrystallization of fine grains (44).

The increased hardness of freshly prepared eutectics of Pb–Sn systems was found to decrease considerably after annealing (49). Eutectic alloys are more sensitive to corrosion, because in the eutectics the metals are in a somewhat activated or reactivated state (49). It is thought that the displacement of the electrons into higher orbitals facilitate their transfer to a third component, such as oxygen, which is an active agent in corrosion. One should also bear in mind that different polymorphic forms in the solid dispersion may also have different chemical stabilities (47).

Aging Effects of Solid Solution—The most important aging effect from solid solutions is the precipitation from supersaturated solid solutions along with the subsequent changes of physical–chemical properties (33, 34, 54, 55, 63).

The precipitation (also called decomposition or demixing) from a solid solution occurs when the concentration of the solute exceeds its equilibrium solubility. As shown in Figs. 5 and 6, the solubility in the continuous or discontinuous solid solution may decrease with decreasing temperature. When a mixture within the solid solution range at high temperature is quenched from the melt to ambient temperature, a

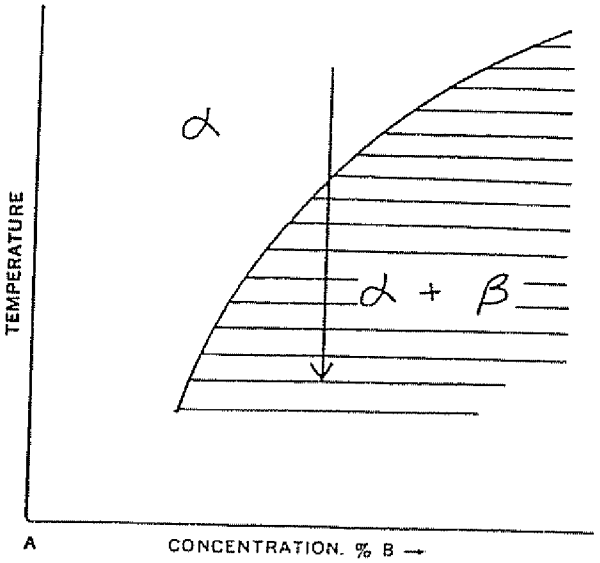


Figure 15—*Phase relation for precipitation. The solid phase, β, precipitates from the solid solution, α, on cooling (arrow) (from* Reference 55, *p. 392, reprinted with permission).*

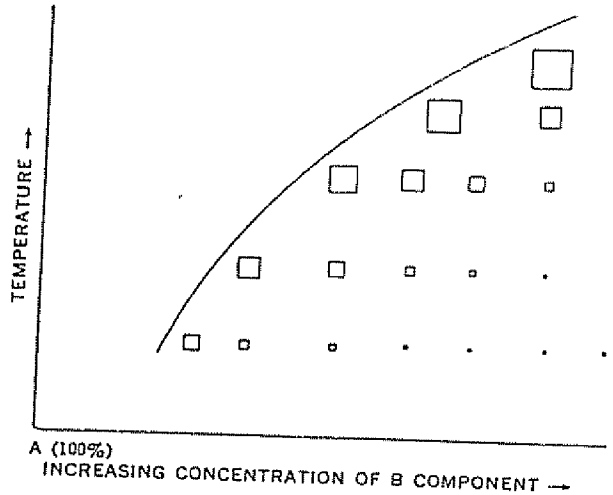


Figure 16—*Diagram illustrating relative nuclei and particle size of precipitation from supersaturated solid solutions at various temperatures and compositions (from* Reference 55, *p. 398, reprinted with permission).*

metastable solid solution is usually obtained. Such excess solute is bound to precipitate out in order to reduce the total free energy of the mixture to a minimum. The phase relations for precipitation are schematically shown in Fig. 15, in which the supersaturated α-phase is transformed into the saturated α-phase and β-solid phase. The β-phase may be a pure crystalline solute, B, or a saturated solid solution of the other component, A, in the B component. The percentage of precipitation can be calculated according to the tieline or lever rule (34, 54, 55).

The particle size and the rate of precipitation certainly have a critical influence upon the dissolution behavior of the dispersed drug. Based on nucleation and growth theory, the relative size of stable nuclei and subsequent precipitation are expected to vary with the composition and storage temperature (Fig. 16). The rate of precipitation is a function of time. After an initial delay of nucleation, it usually proceeds rapidly and finishes slowly (54, 124). A typical example of the precipitation of carbon from an iron–carbon alloy annealed at 76° is shown in Fig. 17. The rate of precipitation also varies with temperature (Fig. 18). The rate is slow at very low temperatures because the diffusion rate of molecules is very low. The precipitation rate is also very low at temperatures just below the solvus line. In this case, the solution is only slightly supersaturated, and the free energy decrease resulting from the precipitation is very small. The nucleation rate is accordingly slow, although the diffusion rate at these high temperatures is high. The maximum precipitation rate, therefore, lies at an intermediate temperature as a compensated result of moderate diffusion and nucleation rates.

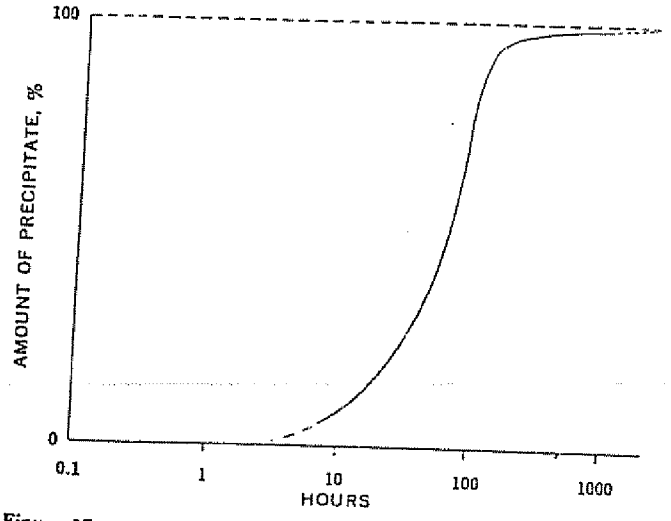


Figure 17—*Amount of precipitate as a function of time in an iron–carbon alloy (0.018% carbon) allowed to precipitate from a supersaturated solution at 76° (from* Reference 54, *p. 239, reprinted with permission).*

The presence of precipitation is usually detected by X-ray diffraction (54, 55, 122, 124, 129, 141–143), X-ray small-angle scattering (141), and electron microscopy (54, 55, 124, 129, 141, 143, 144). A change of lattice parameter of the solvent component after aging is considered as definite evidence of precipitation (55). As discussed previously, the capability of X-ray diffractometry may be handicapped by small particle-size effects. Diffraction from particle sizes well below 0.01 μ may not be detected (145). The appearance of second-phase particles in electron microscopy is also indicative of the occurrence of precipitation. The dissolution-rate method was also recently proposed to study precipitation (68).

The effect of precipitation from supersaturated solid solutions on the age-hardening of alloys is well known (34, 54, 55). The extent of this effect is proportional to the amount precipitated. Therefore, the hardening effect is also a function of composition, aging temperature, and time. Holding or aging the preparations for too long a period at a given temperature may also cause them to lose their hardness. This effect is known as overaging (54). The implications of age-hardening on the overall performance criteria (such as dissolution, disintegration, and tableting) of pharmaceutical solid dispersions remain to be further investigated. In addition to the hardening effect, the precipitation also has caused intergranular corrosion with changes in electrical properties, heat resistance, and specific density (55).

Aging Effects of Glass Solution—Since a glass solution is a metastable form, it may be subjected to aging transformation, yielding a more stable form. This may take place rapidly or extremely slowly, as in the case of untreated ordinary window glass kept at room temperature. Small-angle X-ray scattering and electron microscope methods were used to study the kinetics of a metastable amorphous phase separation from CaO–MgO–SiO_2 glass at 825° (146). The growth of amorphous particles was found to be rate limited by the diffusion process. Their average radius is proportional to the square root of annealing time. The crystallization of iopanoic acid and chloramphenicol palmitate dispersed in polyvinylpyrrolidone 10,000 (5% w/w) was detected by polarizing microscope visualization of crystal needles in unpulverized and pulverized samples. These samples were kept at ambient temperature for several months (41). The effect of such precipitation on the dissolution rate should be further studied.

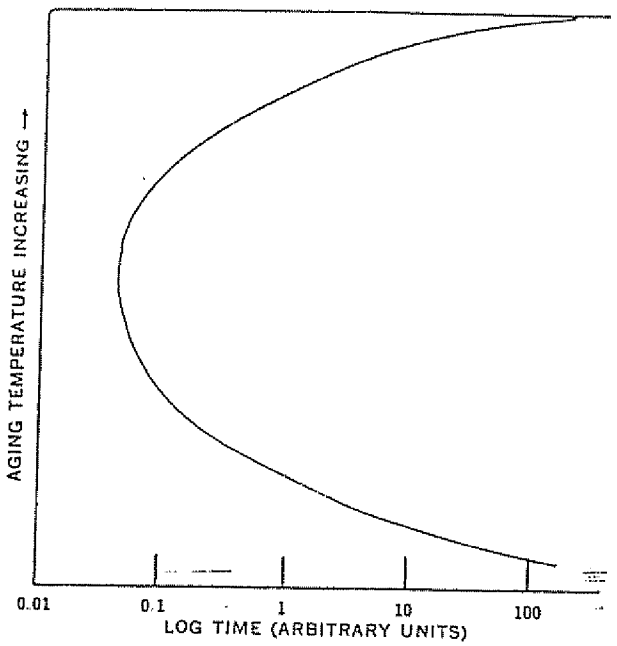


Figure 18—*Diagram illustrating the time for 100% of precipitation from a supersaturated solid solution as a function of aging temperature (from* Reference 54, *p. 240, reprinted with permission).*

Aging Effects of Metastable Polymorphic Forms in Solid Dispersions—The amorphous and other metastable crystalline forms of the dispersed drug in solid dispersions are also subject to aging changes. The importance of this aspect can be seen from the marked difference of dissolution and absorption characteristics between various polymorphic forms of drugs (47). Metastable forms may range from being extremely stable to extremely unstable. Diamond, a crystalline form of carbon, is a good example of the first case. Amorphous form and Form C of chloramphenicol palmitate are examples of the latter case (127).

The methodology for the detection of polymorphic transitions was well reviewed (47). Recently, X-ray diffraction techniques were utilized to study the kinetics of the transformation of amorphous sulfathiazole dispersed in urea at eutectic compositions and their effect on the dissolution rate (56).

REVIEW OF *IN VIVO* STUDIES

Sulfathiazole–Urea Systems—The potential of pharmaceutical applications of solid dispersions was early demonstrated in the human studies of the sulfathiazole–urea system (17). The oral administration of the solidified "eutectic mixture" resulted in a faster and higher rate of absorption than the 50–100-mesh sulfathiazole particles alone on the basis of blood levels and urinary excretion data. The cumulative excretion of the drug and its metabolites in 8 hr. was also 23% higher from the "eutectic mixture." The excretion rate data are shown in Fig. 19. The presence of the urea was found not to interfere with the absorption of the sulfathiazole. The *in vitro* dissolution rate of sulfathiazole will probably be diminished in the presence of urea due to its decreasing solubility in the aqueous solution of urea (17).

Chloramphenicol–Urea Systems—In oral suspension studies in rabbits (51), the solid dispersion of 20% chloramphenicol–80% urea produced a faster and higher absorption in the 1st hr. than the pure chloramphenicol with a similar particle-size distribution (50–100 mesh). The peak value was about 70% higher for the solid dispersion. However, the total areas under the blood level–time curve from both dosage forms were almost the same. When administered in capsule form, the solid dispersion produced a much higher blood level in the first 4 hr. In the first 2 hr., the ratio of blood levels gave a threefold difference. Such marked difference in absorption characteristics obtained in both suspension and capsule forms has not been entirely explained. It is believed that in the capsule case, this difference is a reflection of better wetting and dispersion of solid in the urea system than in the pure, poorly soluble chloramphenicol system. These advantages would become less significant when administered in suspension form. The solid dispersion with eutectic composition (76% chloramphenicol–24% urea) was shown to be inferior in absorption than the pure compound when studied in either the capsule or suspension form.

The finer particle sizes of chloramphenicol obtained in the low concentration of the mixture were proposed to have contributed to its better absorption and the attainment of supersaturation from the lower concentration dispersed form (50, 51). Unfortunately, these studies were conducted on rabbits whose rate of stomach emptying in the feeding and fasting state differs markedly from man. The lack of suitability of using rabbits in evaluating drug absorption was recently raised by Chiou *et al.* (147).

Reserpine–Bile Acid Coprecipitates—A more rapid onset of blepharoptotic activity as well as a significantly increased potency relative to reserpine base was shown in mice after oral administration of reserpine–deoxycholic acid coprecipitates (39). The enhancement generally increased as the concentration of reserpine in the coprecipitates decreased. The only exception was that of the lowest concentration dispersion studied (1:32 molar amounts of reserpine–desoxycholic acid). The physical mixture was also more potent than the reserpine base. These findings were attributed to the enhancement of oral absorption of the drug dispersed

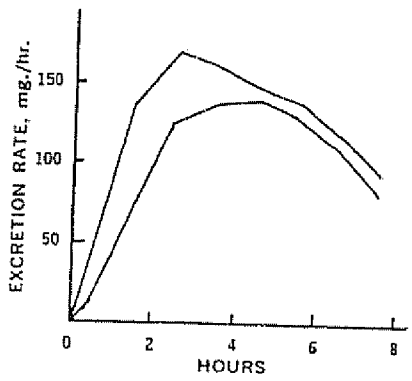


Figure 19—*Average excretion rates of total sulfathiazole in urine after administration of 2 g. of sulfathiazole as a eutectic mixture (top curve) and pure compound (lower curve) to a human subject (from* Reference 17, *Fig. 11, reprinted with permission).*

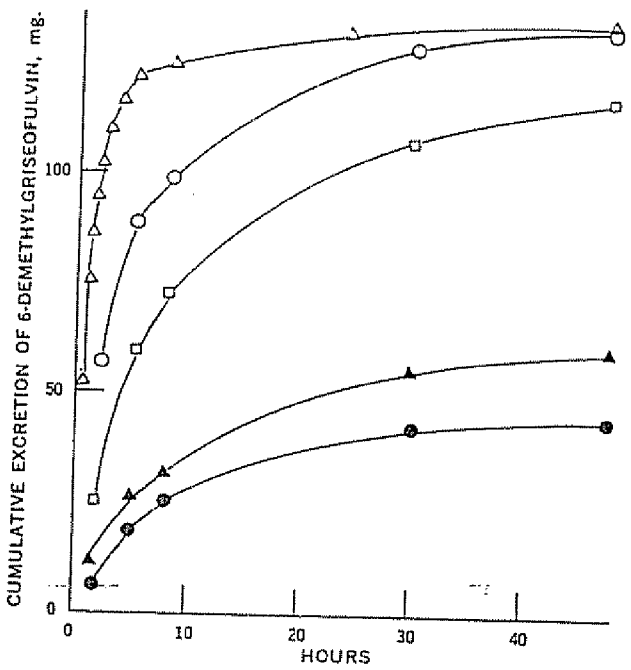


Figure 20—*Average cumulative urinary excretion of 6-demethylgriseofulcin, a major metabolite, after oral and intravenous doses of griseofulcin in dogs. Key: △, intravenous dose; ○, griseofulcin in polyethylene glycol 400 solution; □, griseofulcin dispersed in polyethylene glycol 6000 (10% w/w); ▲, commercial capsule of micronized griseofulcin; and ●, commercial tablet of micronized griseofulcin (all data corrected for 250-mg. dose) (from* Reference 27, *Fig. 2, reprinted with permission).*

in the bile acid. A rank correlation with the *in vitro* dissolution rate was found (88). Similar phenomena of increased blepharoptotic activity in mice were also reported for the reserpine coprecipitates with other bile acids (87). The general application of drug coprecipitates in increasing drug absorption remains to be explored.

Griseofulvin–Polyethylene Glycol Polymers—In none of the *in vivo* studies of three solid dispersion systems discussed here were comparisons made with micronized or microcrystalline powders of pure drugs. The solid dispersion approach will certainly appear unique and valuable if it proves to yield better oral absorption than that obtainable with the commercially available micron-size powders. Such critical evaluation was first carried out in dogs (27) and man (28, 29) for micronized griseofulvin and griseofulvin dispersed in polyethylene glycol.

In the dog studies, the total areas under the blood concentration curves in the first 8 hr. for the micronized griseofulvin, either in tablet or capsule form, were found to be approximately only 25% of those obtained from capsule forms of 10% griseofulvin–90% polyethylene glycol prepared by melting methods. By analyzing the total excretion of the major metabolite in 48 hr., it was found that approximately 88% of dispersed griseofulvin, 45% of micronized griseofulvin in capsule form, and 33% of micronized griseofulvin in tablet form were absorbed. The griseofulvin dissolved in polyethylene glycol 400 was found to be completely absorbed. Their cumulative excretion plots are shown in Fig. 20. From the analysis of the excretion rate data, it was found that oral absorption of griseofulvin in dogs could proceed for more than 40 hr. The amounts absorbed were shown to correlate linearly with the logarithm of the *in vitro* dissolution rates. The solid dispersion of 5% griseofulvin–95% polyethylene glycol 4000 also produced about fourfold the blood area in the first 8 hr. than did the micronized griseofulvin in a dog (12). In a preliminary study, the presence of polyethylene glycol 4000 in a physical mixture was found not to affect the oral absorption of micronized griseofulvin (12).

To test its practical application, the absorption studies were further carried out in human subjects. The 10 and 20% griseofulvin dispersions in polyethylene glycol 6000 were found to be almost completely absorbed in eight trials, while only 43% of micronized griseofulvin was absorbed. More strikingly, the absorption from dispersed forms was almost complete within 2 hr. after administration. The absorption from the micronized product was found to continue for 30–80 hr. after dosing. The average cumulative excretion of urinary metabolites (6-demethylgriseofulvin and its glucuronide) obtained from administration of various forms is plotted in Fig. 21. The rapid and complete absorption of the insoluble antibiotic in man was mainly attributed to the molecular and colloidal dispersion of the drug in a highly water-soluble carrier. It is predicted that the polyethylene glycol can act as one

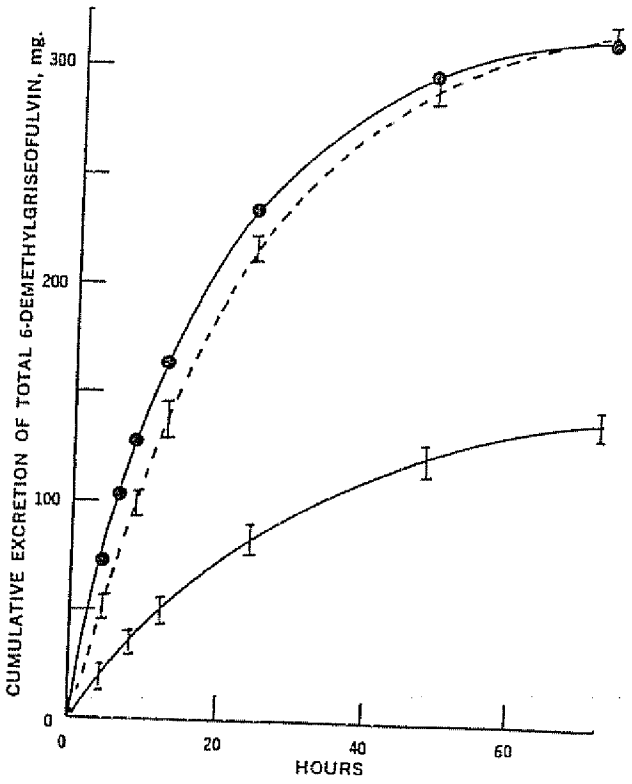


Figure 21—*Cumulative total 6-demethylgriseofulcin urinary excretion data after intravenous and oral administration of griseofulcin to two human subjects (intravenous data only for a subject; others are mean values of eight trials). Key: ●, intravenous dose; - - -, griseofulcin dispersed in polyethylene glycol 6000 (10 and 20% w/w); and ——, tablets of micronized griseofulcin (all data corrected for 500-mg. dose) (from* Reference 28, *reprinted with permission).*

of the ideal universal carriers for most poorly soluble drugs.

MISCELLANEOUS APPLICATION

A unique method in formulating a liquid drug or chemical in a solid dosage form was recently introduced by Chiou and Smith (40). A liquid drug such as methyl salicylate, vitamin E, clofibrate, benzyl benzoate, and benzonatate was mixed by mechanical stirring with the melted liquid of polyethylene glycol 6000 at a temperature below 70°. The mixture was then rapidly cooled, and the resultant "solid" mass was pulverized, encapsulated, and tableted. The method is particularly valuable for drugs with low therapeutic doses because the maximum concentration that can be incorporated into a solid form only ranged between 5 and 10% (w/w). It is believed that other thermoplastic polymers with low melting points can also function as carriers for such purposes.

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